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 NEWS  2          "Ask CAS" for self-help around the clock
 NEWS  3  FEB 27  New STN AnaVist pricing effective March 1, 2006
 NEWS  4  MAY 10  CA/CAplus enhanced with 1900-1906 U.S. patent records
 NEWS  5  MAY 11  KOREAPAT updates resume
 NEWS  6  MAY 19  Derwent World Patents Index to be reloaded and enhanced
 NEWS  7  MAY 30  IPC 8 Rolled-up Core codes added to CA/CAplus and
                  USPATFULL/USPAT2
 NEWS  8  MAY 30  The F-Term thesaurus is now available in CA/CAplus
 NEWS  9  JUN 02  The first reclassification of IPC codes now complete in
                  INPADOC
 NEWS 10  JUN 26  TULSA/TULSA2 reloaded and enhanced with new search and
                  and display fields
 NEWS 11  JUN 28  Price changes in full-text patent databases EPFULL and PCTFULL
 NEWS 12  JUl 11  CHEMSAFE reloaded and enhanced
 NEWS 13  JUl 14  FSTA enhanced with Japanese patents
 NEWS 14  JUl 19  Coverage of Research Disclosure reinstated in DWPI
 NEWS 15  AUG 09  INSPEC enhanced with 1898-1968 archive
 NEWS 16  AUG 28  ADISCTI Reloaded and Enhanced
 NEWS 17  AUG 30  CA(SM)/CAplus(SM) Austrian patent law changes
 NEWS 18  SEP 11  CA/CAplus enhanced with more pre-1907 records
 NEWS 19  SEP 21  CA/CAplus fields enhanced with simultaneous left and right
                  truncation
 NEWS 20  SEP 25  CA(SM)/CAplus(SM) display of CA Lexicon enhanced
 NEWS 21  SEP 25  CAS REGISTRY(SM) no longer includes Concord 3D coordinates
 NEWS 22  SEP 25  CAS REGISTRY(SM) updated with amino acid codes for pyrrolysine
 NEWS 23  SEP 28  CEABA-VTB classification code fields reloaded with new
                  classification scheme

 NEWS EXPRESS  JUNE 30 CURRENT WINDOWS VERSION IS V8.01b, CURRENT
               MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
               AND CURRENT DISCOVER FILE IS DATED 26 JUNE 2006.

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 NEWS X25      X.25 communication option no longer available

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* * * * * * * * * * * * * * * STN Columbus * * * * * * * * * * * * * * * *
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FILE 'HOME' ENTERED AT 15:28:59 ON 11 OCT 2006

=> file caplus, bioeng, biotechno, biotechds, esbiobase
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                                                      ENTRY   SESSION
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=> s( MN-14 and antibody)
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=> s (mn-14 and antibody)
L1         112 (MN-14 AND ANTIBODY)

=> s l1 and (cytotoxic agent)
L2           7 L1 AND (CYTOTOXIC AGENT)

=> duplicate remove l2
DUPLICATE PREFERENCE IS 'CAPLUS, BIOTECHDS, ESBIOBASE'
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PROCESSING COMPLETED FOR L2
L3            5 DUPLICATE REMOVE L2 (2 DUPLICATES REMOVED)

=> d l3 bib abs 1-5

L3   ANSWER 1 OF 5  CAPLUS  COPYRIGHT 2006 ACS on STN  DUPLICATE 1
AN   2004:333598  CAPLUS
DN   140:373894
TI   CEA-specific monoclonal antibodies or fragments with therapeutic
     agents for treating CEA-expressing cancers and diseases
IN   Goldenberg, David M.; Hansen, Hans J.
PA   Immunomedics, Inc., USA
SO   PCT Int. Appl., 88 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 2
     PATENT NO.          KIND   DATE        APPLICATION NO.        DATE
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PI   WO 2004032962        A1    20040422    WO 2002-US32307        20021011
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             CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
             GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
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     AU 2002332087        A1     20040504   AU 2002-332087         20021011
     EP 1558284           A1     20050803   EP 2002-769028         20021011
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     CN 1708317           A      20051214   CN 2002-830006         20021011
     JP 2006507263        T2     20060302   JP 2004-542990         20021011
     CA 2501616           AA     20040422   CA 2003-2501616        20031008
     WO 2004032857        A2     20040422   WO 2003-US31801        20031008
     WO 2004032857        C1     20050407
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     US 2004191248        A1     20040930   US 2003-680734         20031008
     EP 1572131           A2     20050914   EP 2003-774636         20031008
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     JP 2006521286        T2     20060921   JP 2005-501118         20031008
PRAI US 2002-416531P      P      20021008
     WO 2002-US32307      W      20021011
     US 2003-467161P      P      20030502
     WO 2003-US31801      W      20031008
AB   The present invention provides a composition comprising naked humanized,
     chimeric and human Class III anti-CEA monoclonal antibody and a
     therapeutic agent, which is useful for treatment of CEA-expressing cancers
     and other diseases, and methods of treatment using this composition  The
     anti-CEA monoclonal antibody or fragment is a humanized or
     chimeric MN-14 antibody or fragment or fully
     human MN-14 antibody or fragment.
RE.CNT  2     THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
              ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3   ANSWER 2 OF 5  CAPLUS  COPYRIGHT 2006 ACS on STN  DUPLICATE 2
AN   2004:331925  CAPLUS
DN   140:355848
TI   humanized or chimeric derivatives of murine monoclonal anti-CEA
     antibody MN-14 and conjugates for cancer
     therapy
IN   Goldenberg, David M.; Hansen, Hans J.
PA   Immunomedics, Inc., USA
SO   PCT Int. Appl., 121 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 2
     PATENT NO.          KIND   DATE       APPLICATION NO.        DATE
     ---------------     ----   --------   --------------------   --------
PI   WO 2004032857        A2     20040422   WO 2003-US31801        20031008
     WO 2004032857        C1     20050407
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          CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE,
          GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK,
          LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ,
          OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM,
          TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
      RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
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          FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,
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     WO 2004032962          A1     20040422    WO 2002-US32307        20021011
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          CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
          GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
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          FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF,
          CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
     CA 2501616             AA     20040422    CA 2003-2501616        20031008
     AU 2003282752          A1     20040504    AU 2003-282752         20031008
     EP 1572131             A2     20050914    EP 2003-774636         20031008
      R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
          IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK
     JP 2006521286          T2     20060921    JP 2005-501118         20031008
PRAI US 2002-416531P        P      20021008
     WO 2002-US32307        A      20021011
     US 2003-467161P        P      20030502
     WO 2003-US31801        W      20031008
AB   The present invention provides a composition comprising naked humanized or
     chimeric murine monoclonal antibody MN-14
     and a therapeutic agent, which is useful for treatment of CEA expressing
     cancers and other diseases, and methods of use in treatment using this
     composition

L3   ANSWER 3 OF 5  CAPLUS  COPYRIGHT 2006 ACS on STN
AN   2003:320021  CAPLUS
DN   138:336427
TI   Direct targeting binding multivalent monospecific proteins of human
IN   Rossi, Edmund; Chang, Chien-Hsing Ken; Goldenberg, David M.
PA   IBC Pharmaceuticals, USA; Immunomedics Inc.
SO   PCT Int. Appl., 62 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 2
     PATENT NO.             KIND   DATE        APPLICATION NO.        DATE
     ---------------        ----   --------    --------------------   --------
PI   WO 2003033654          A2     20030424    WO 2002-US32718        20021015
     WO 2003033654          A3     20031113
      W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
          CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
          GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
          LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
          PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,
          UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
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          KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
          FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF,
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     CA 2463672             AA     20030424    CA 2002-2463672        20021015
     US 2003148409          A1     20030807    US 2002-270073         20021015
     EP 1448780             A2     20040825    EP 2002-782156         20021015
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         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
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     JP 2005507659         T2     20050324    JP 2003-536384         20021015
     CN 1604966            A      20050406    CN 2002-825068         20021015
     BR 2002013303         A      20050607    BR 2002-13303          20021015
PRAI US 2001-328835P       P      20011015
     US 2001-341881P       P      20011221
     US 2002-345641P       P      20020108
     US 2002-404919P       P      20020822
     WO 2002-US32718       W      20021015
AB   The present invention relates to multivalent, monospecific binding
     proteins.  These binding proteins comprise two or more binding sites,
     where each binding site specifically binds to the same type of target
     cell, and preferably with the same antigen on such a target cell.  The
     present invention further relates to compns. of monospecific diabodies,
     triabodies, and tetrabodies, and to recombinant vectors useful for the
     expression of these functional binding proteins in a microbial host.  Also
     provided are methods of using invention compns. in the treatment and/or
     diagnosis of tumors.

L3    ANSWER 4 OF 5  Elsevier BIOBASE  COPYRIGHT 2006 Elsevier Science B.V. on
      STN
AN    1999240226   ESBIOBASE
TI    Radioimmunotherapy of small volume disease of colorectal cancer
      metastatic to the liver: Preclinical evaluation in comparison to standard
      chemotherapy and initial results of a phase I clinical study
AU    Behr T.M.; Salib A.L.; Liersch T.; Behe M.; Angerstein C.; Blumenthal
      R.D.; Fayyazi A.; Sharkey R.M.; Ringe B.; Becker H.; Wormann B.;
      Hiddemann W.; Goldenberg D.M.; Becker W.
CS    T.M. Behr, Department of Nuclear Medicine, Georg-August-University of
      Gottingen, RobertKoch-Strasse 40, D-37075 Gottingen, Germany.
      E-mail: tmbehr@med.uni-goettingen.de
SO    Clinical Cancer Research, (1999), 5/10 SUPPL. (3232s-3242s), 43
      reference(s)
      CODEN: CCREF4  ISSN: 1078-0432
DT    Journal; Conference Article
CY    United States
LA    English
SL    English
AB    At the time of surgery, occult metastases (micrometastases) are present
      in more than 50% of colorectal cancer patients, and the liver is the most
      frequent site of apparent metastatic disease. Frequently, adjuvant
      chemotherapy is unable to prevent tumor recurrence. Thus, novel
      therapeutic strategies are warranted. The aim of this study was to
      establish a model of human colon cancer metastatic to the liver of nude
      mice, to assess, in this setting, the therapeutic efficacy of
      radioimmunotherapy (RAIT) compared to standard chemotherapy and to
      evaluate, in a Phase I/II trial, the toxicity and therapeutic efficacy of
      RAIT in colorectal cancer patients with small volume disease metastatic
      to the liver. Multiple liver metastases of the human colon cancer cell
      line G W-39 were induced by intrasplenic injection of a 10% tumor cell
      suspension. Whereas controls were left untreated, therapy was initiated
      on day 10 or 20 after tumor inoculation with the .sup.1.sup.3.sup.1I-
      labeled, low affinity anticarcinoembryonic antigen (anti-CEA) monoclonal
      antibody (MAb), F023C5 (K(a) = 10.sup.7 liters/mol), or the
      high-affinity anti- CEA MAb, MN-14 (K(a) = 10.sup.9
      liters/mol), or chemotherapy (5- fluorouracil/leucovorin (folinic acid)
      versus irinotecan) at their respective maximum tolerated doses (MTDs).
      Twelve colorectal cancer patients with small volume disease metasiatic to
      the liver (all lesions <=2.5 cm) were entered into a mCi/m.sup.2-based
      Phase I dose escalation study with .sup.1.sup.3.sup.1I-labeled humanized
      version of MN-14, hMN-14. The patients were given
      single injections, starting at 50 mCi/m.sup.2 and escalating in
      10-mCi/m.sup.2 increments. The MTD was defined as the dose level at which
     <=1 of 6 patients develop grade 4 myelotoxicity. In the mice, untreated
     controls died from rapidly progressing hepatic metastases at 6-8 weeks
     after tumor inoculation. The life span of mice treated with
     5-fluoroaracil/leucovorin was prolonged for only 1- 3 weeks, whereas
     irinotecan led to a 5-8-week prolongation. In contrast, at their
     respective MTDs, the .sup.1.sup.3.sup.1I-labeled low-affinity anti-CEA
     MAb, F023C5, led to a 20% permanent cure rate, and the high affinity MAb,
     MN-14, led to an 80% permanent cure rate, when therapy
     was initiated at 10 days after tumor inoculation. In the 20-day-old tumor
     stage, although it prolonged life, .sup.1.sup.3.sup.1I-F023C5 was unable
     to achieve cures, whereas .sup.1.sup.3.sup.1I-MN-14
     was still successful in 20%. Histologically, no remaining viable tumor
     cells could be demonstrated in these animals surviving >6 months. In
     patients, the MTD was reached at 60 mCi/m.sup.2 of hMN-14 (at 70
     mCi/m.sup.2, two of three grade 4 myelotoxicities). Of 11 assessable
     patients, 2 had partial remissions (corresponding to an objective
     response rate of 18%), and 5 (45%) had minor/mixed responses or
     experienced stabilization of previously rapidly progressing disease.
     These data suggest that in small volume disease, RAIT may be superior to
     conventional chemotherapy. Antibodies of higher affinity seem
     to be clearly superior. The clinical response rates in patients with
     small volume disease are encouraging, being comparable to the response
     rates of conventional chemotherapeutic regimens but with fewer side
     effects. Ongoing studies will show whether treatment at the MTD will
     further improve therapeutic results.

L3   ANSWER 5 OF 5  CAPLUS  COPYRIGHT 2006 ACS on STN
AN   1996:401716  CAPLUS
DN   125:56229
TI   CDR-grafted type III anti-CEA humanized mouse monoclonal
     antibodies
IN   Hansen, Hans J.; Armour, Kathryn L.
PA   Immunomedics, Inc., USA
SO   PCT Int. Appl., 61 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 1
     PATENT NO.          KIND   DATE        APPLICATION NO.        DATE
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PI   WO 9611013           A1    19960418    WO 1995-US11964        19950928
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     CA 2200868           AA    19960418    CA 1995-2200868        19950928
     AU 9537196           A1    19960502    AU 1995-37196          19950928
     AU 689331            B2    19980326
     EP 783313            A1    19970716    EP 1995-935020         19950928
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     JP 3437580           B2    20030818
     AU 9873209           A1    19980813    AU 1998-73209          19980625
     AU 723073            B2    20000817
     US 2002018750        A1    20020214    US 1999-253794         19990222
     US 6676924           B2    20040113
     US 2005089538        A1    20050428    US 2004-755382         20040113
PRAI US 1994-318157       A     19941005
     WO 1995-US11964      W     19950928
     US 1999-253794       A1    19990222
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AB   A humanized monoclonal antibody, comprising the
     complementarity-determining regions of a parental murine Class III, anti-CEA
     monoclonal antibody engrafted to the framework regions of a
     heterologous antibody, wherein the humanized monoclonal
     antibody retains the binding specificity of, but is less
     immunogenic in a heterologous host than, the parental murine monoclonal
     antibody.  A preferred murine Class III, anti-CEA monoclonal
     antibody is the MN-14 antibody and
     the preferred heterologous antibody is from a human.  Also
     provided are DNA constructs and vectors for producing the humanized
     monoclonal antibodies, and diagnostic and therapeutic conjugates
     using same.  The humanized monoclonal antibody is useful for
     tumor, especially colon cancer, diagnosis.


=> d his

     (FILE 'HOME' ENTERED AT 15:28:59 ON 11 OCT 2006)

     FILE 'CAPLUS, BIOENG, BIOTECHNO, BIOTECHDS, ESBIOBASE' ENTERED AT
     15:29:24 ON 11 OCT 2006
L1          112 S (MN-14 AND ANTIBODY)
L2            7 S L1 AND (CYTOTOXIC AGENT)
L3            5 DUPLICATE REMOVE L2 (2 DUPLICATES REMOVED)

=> s l2 and CPT-11
L4            3 L2 AND CPT-11

=> d l4 bib abs 1-3

L4   ANSWER 1 OF 3  CAPLUS  COPYRIGHT 2006 ACS on STN
AN   2004:331925  CAPLUS
DN   140:355848
TI   humanized or chimeric derivatives of murine monoclonal anti-CEA
     antibody MN-14 and conjugates for cancer
     therapy
IN   Goldenberg, David M.; Hansen, Hans J.
PA   Immunomedics, Inc., USA
SO   PCT Int. Appl., 121 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 2
     PATENT NO.          KIND   DATE         APPLICATION NO.        DATE
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PI   WO 2004032857        A2    20040422     WO 2003-US31801        20031008
     WO 2004032857        C1    20050407
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
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             TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
             KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
             FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,
             BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
     WO 2004032962        A1    20040422     WO 2002-US32307         20021011
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
             GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
             LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
             PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,
             UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
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            KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
            FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF,
            CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
     CA 2501616          AA    20040422    CA 2003-2501616        20031008
     AU 2003282752       A1    20040504    AU 2003-282752         20031008
     EP 1572131          A2    20050914    EP 2003-774636         20031008
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            IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK
     JP 2006521286       T2    20060921    JP 2005-501118         20031008
PRAI US 2002-416531P     P     20021008
     WO 2002-US32307     A     20021011
     US 2003-467161P     P     20030502
     WO 2003-US31801     W     20031008
AB   The present invention provides a composition comprising naked humanized or
     chimeric murine monoclonal antibody MN-14
     and a therapeutic agent, which is useful for treatment of CEA expressing
     cancers and other diseases, and methods of use in treatment using this
     composition

L4   ANSWER 2 OF 3  CAPLUS  COPYRIGHT 2006 ACS on STN
AN   2003:320021  CAPLUS
DN   138:336427
TI   Direct targeting binding multivalent monospecific proteins of human
IN   Rossi, Edmund; Chang, Chien-Hsing Ken; Goldenberg, David M.
PA   IBC Pharmaceuticals, USA; Immunomedics Inc.
SO   PCT Int. Appl., 62 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 2
     PATENT NO.          KIND  DATE        APPLICATION NO.        DATE
     ---------------     ----  --------    --------------------   --------
PI   WO 2003033654        A2   20030424    WO 2002-US32718        20021015
     WO 2003033654        A3   20031113
        W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
            CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
            GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
            LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
            PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,
            UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
        RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
            KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
            FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF,
            CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
     CA 2463672          AA    20030424    CA 2002-2463672        20021015
     US 2003148409       A1    20030807    US 2002-270073         20021015
     EP 1448780          A2    20040825    EP 2002-782156         20021015
        R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
            IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK
     JP 2005507659       T2    20050324    JP 2003-536384         20021015
     CN 1604966          A     20050406    CN 2002-825068         20021015
     BR 2002013303       A     20050607    BR 2002-13303          20021015
PRAI US 2001-328835P     P     20011015
     US 2001-341881P     P     20011221
     US 2002-345641P     P     20020108
     US 2002-404919P     P     20020822
     WO 2002-US32718     W     20021015
AB   The present invention relates to multivalent, monospecific binding
     proteins.  These binding proteins comprise two or more binding sites,
     where each binding site specifically binds to the same type of target
     cell, and preferably with the same antigen on such a target cell.  The
     present invention further relates to compns. of monospecific diabodies,
     triabodies, and tetrabodies, and to recombinant vectors useful for the
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expression of these functional binding proteins in a microbial host. Also provided are methods of using invention compns. in the treatment and/or diagnosis of tumors.

L4 ANSWER 3 OF 3 BIOTECHDS COPYRIGHT 2006 THE THOMSON CORP. on STN
AN 2004-13886 BIOTECHDS
TI Treating non-medullary or medullary thyroid carcinoma, involves administering to subject, either concurrently or sequentially, anti-carcinoembryonic antigen antibody or its fragment and therapeutic agent;
antibody against antigen for use in disease therapy
AU GOLDENBERG D M; HANSEN H J
PA IMMUNOMEDICS INC
PI WO 2004032857 22 Apr 2004
AI WO 2003-US31801 8 Oct 2003
PRAI US 2003-467161 2 May 2003; US 2002-416531 8 Oct 2002
DT Patent
LA English
OS WPI: 2004-340797 [31]
AN 2004-13886 BIOTECHDS
AB DERWENT ABSTRACT:

NOVELTY - Treating (M1) non-medullary or medullary thyroid carcinoma, comprising administering to a subject, either concurrently or sequentially, an anti-carcinoembryonic antigen (anti-CEA) antibody or its fragment and at least one therapeutic agent, and optionally formulated in a vehicle, is new.

DETAILED DESCRIPTION - Treating (M1) non-medullary or medullary thyroid carcinoma, involves administering to a subject, either concurrently or sequentially, an anti-carcinoembryonic antigen (anti-CEA) antibody or its fragment and at least one therapeutic agent, and optionally formulated in a vehicle. Optionally, (M1) involves treating cancer by: (a) pre-treating a subject suffering from cancer with an anti-CEA antibody or its fragment prior to administration of the non-antibody therapeutic agent; (b) administering to a subject suffering from cancer, prior to administration of the antibody, an agent that activates granulocytes and/or NK cells in order to increase effector function of the antibody; or (c) administering to a subject suffering from cancer, prior to administration of the anti-CEA antibody or fragment, an amount of interferon effective to upregulate CEA expression in tumor cells. INDEPENDENT CLAIMS are also included for: (1) the composition (I) comprising at least one anti-CEA MAb (MAb) or its fragment and at least one therapeutic agent; and (2) an antibody fusion protein (II) comprising at least one CEA binding site and at least one other binding site for the same or different antigen.

BIOTECHNOLOGY - Preferred Method: In (M1), the anti-CEA MAb is a Class I, Class II or Class III anti-CEA MAb. The anti-CEA MAb is a Class I or Class II anti-CEA MAb, which is reactive with granulocytes and is a monovalent form of the MAb. The anti-CEA MAb or its fragment is humanized, where the humanized MAb retains substantially the anti-CEA binding specificity of a murine anti-CEA MAb. The anti-CEA MAb or its fragment is a chimeric MAb, which retains substantially the anti-CEA binding specificity of murine anti-CEA MAb. The anti-CEA MAb or its fragment is a MN-14 antibody or its fragment. The MN-14 MAb or its fragment comprises the complementarity-determining regions (CDRs) of a murine MN-14 MAb, where the CDRs of the light chain variable region of the MN-14 antibody comprises CDR1 having an amino acid sequence of Lys-Ala-Ser-Gln-Asp-Val-Gly-Thr-Ser-Val-Ala, CDR2 having an amino acid sequence of Trp-Thr-Ser-Thr-Arg-His-Thr and CDR3 having an amino acid sequence of Gln-Gln-Tyr-Ser-Leu-Tyr-Arg-Ser. The CDRs of the heavy chain variable region of the anti-CEA antibody comprises CDR1, CDR2 and CDR3 having Thr-Tyr-Trp-Met-Ser, Glu-Ile-his-Pro-Asp-Ser-Ser-Thr-Ile-Asn-Tyr-Ala-Pro-Ser-Leu-Lys-Asp and Lys-Tyr-Phe-Gly-Phe-Pro-

Trp-Phe-Ala-Tyr, respectively. The anti-CEA MAb reacts with CEA and is unreactive with normal cross-reactive antigen (NCA) and meconium antigen (MA). The MN-14 MAb or its fragment is a humanized, chimeric or fully human MN-14 antibody or its fragment. The framework regions (FRs) of the light and heavy chain variable regions of the humanized MN-14 antibody or its fragment comprise at least one amino acid substituted from the corresponding FRs of a murine MN-14 MAb. The humanized MN-14 antibody or its fragment comprises at least one amino acid from the corresponding FR of the murine MN-14 antibody, chosen from amino acid residue 24, 28, 30, 48, 49, 74 and 94 of the murine heavy chain variable region designated as KLHuVhAIGA or (hMN-14). The humanized MN-14 antibody or its fragment comprises at least one amino acid from the corresponding FR of the murine MN-14 light chain variable region. The humanized MN-14 antibody or its fragment comprises the light chain variable region as set forth in (hMN-14) and the heavy chain variable region designated as KLHuVhAIGA, 15B (hMN-14) or 16B. The fragment is chosen from F(ab')2, Fab', Fab, Fv and sFV. The therapeutic agent is chosen from humanized, chimeric, human or murine MAb or its fragment chosen from Class I anti-CEA MAb, Class II anti-CEA MAb, Class III anti-CEA MAb, and its fragment, and is administered either concurrently or sequentially in a therapeutically effective amount. The therapeutic agent is either a naked antibody or an antibody conjugated to another therapeutic agent. The therapeutic agent is chosen from naked antibody, cytotoxic agent, a drug, a radionuclide, an immunomodulator, a photoactive therapeutic agent, an immunoconjugate of a CEA or non-CEA antibody, a hormone, or its combination, optionally formulated in a pharmaceutically acceptable vehicle. The therapeutic agent is chosen from humanized, chimeric, human or murine MAb or its fragment reactive with EGP-1, EGP-2 (e.g., 17-1A), IL-6, MUC-1, MUC-2, MUC-3, MUC-4, PAM-4, KC4, TAG-72, EGFR, EGP-2, HER2/neu, BrE3, Le-Y, A3, A33, EP-CAM, AFP, Tn, Thomson-Friedenreich antigens, tumor necrosis antigens, VEGF, tenascin, fibronectin, or other tumor angiogenesis antigens, Ga 733, and its combination, and is administered to the subject either concurrently or sequentially in a therapeutically effective amount. The antibody or its fragment is either naked or conjugated to another therapeutic agent. The therapeutic agent is not DTIC. The cytotoxic agent is a drug or a toxin. The drug possesses the pharmaceutical property chosen from the group consisting of antimitotic, alkylating, antimetabolite, antiangiogenic, apoptotic, alkaloid, COX-2, and antibiotic agents and its combinations. The drug is chosen from nitrogen mustards, ethylenimine derivatives, alkyl sulfonates, nitrosoureas, triazenes, folic acid analogs, anthracyclines, taxanes, COX-2 inhibitors, pyrimidine analogs, purine analogs, antimetabolites, antibiotics, enzymes, epipodophyllotoxins, platinum coordination complexes, vinca alkaloids, substituted ureas, methyl hydrazine derivatives, adrenocortical suppressants, antagonists, endostatin, taxols, camptothecins, doxorubicins and their analogs, and its combination. The toxin is a microbial, plant or animal toxin chosen from ricin, abrin, alpha toxin, saporin, ribonuclease (RNase), DNase I, Staphylococcal enterotoxin-A, pokeweed antiviral protein, gelonin, diphtherin toxin, Psuedomonas exotoxin, and Pseudomonas endotoxin. The immunomodulator is chosen from cytokine, a stem cell growth factor, a lymphotoxin, a hematopoietic factor (e.g., interleukin), a colony stimulating factor (CSF) (e.g., granulocyte-colony stimulating factor (G-CSF) or granulocyte macrophage-colony stimulating factor (GM-CSF)), an interferon (IFN) (e.g., interferons-alpha, -beta, or -gamma), a stem cell growth factor (designated S1 factor), erythropoietin, thrombopoietin and its combination. The lymphotoxin is tumor necrosis factor (TNF). The immunomodulator comprises IL-1, IL-2, IL-3, IL-6, IL-10, IL-12, IL-18, interferon-gamma, TNF-alpha or its combination. The radonuclide has an energy between 20-10000 keV.74. The radionuclide is chosen from 125I, 131I, 90Y, 88Y, 225Ac, 177Lu, 188Re, 186Re, and its combination. The photoactive therapeutic agent is a chromogen or dye. The alkylating agent is decarbazine. The Class III anti-CEA MAb or its fragment is humanized, which retains substantially the Class III anti-CEA binding specificity of a murine Class III anti-CEA MAb. The Class III anti-CEA MAb or is fragment is a chimeric MAb, which retains substantially the Class III anti-CEA binding specificity of murine Class III anti-CEA MAb. The Class III anti-CEA MAb or its fragment is a MN-14 antibody or its fragment. The humanized Class III anti-CEA antibody or its fragment is a humanized MN-14 antibody or its fragment. The therapeutic agent is chosen from humanized, chimeric, human or murine MAb or its fragment chosen from a Class I anti-CEA MAb, Class II anti-CEA MAb, Class III anti-CEA MAb, and its fragment, and is administered either concurrently or sequentially in a therapeutically effective amount. The therapeutic agent is either a naked antibody or an antibody conjugated to another therapeutic agent. The therapeutic agent is CPT-11. The anti-CEA antibody or its fragment administered prior to administration of CPT-11. The anti-CEA antibody or its fragment is administered around 3 days prior to administration of CPT-11. The therapeutic agent is DTIC, oxaliplatin or 5-flourouracil/leucovorin. The anti-CEA antibody is hMN-14. The therapeutic agent is CPT-11 or GM-CSF. Preferred Composition: In (I), the anti-CEA MAb or its fragment is a fully human MAb, which retains substantially the anti-CEA binding specificity of murine anti-CEA MAb. The chimeric MN-14 antibody or its fragment comprises the light chain variable region designated as murine MN-14 Vk and the heavy chain variable region designated as murine MN-14 VH. The fragment is chosen from F(ab')2, Fab', Fab, Fv and scFv. The combination comprises vincristine, doxorubicin, DTIC and cyclophosphamide. The therapeutic agent is a naked antibody or an immunoconjugate. Preferred Fusion protein: In (II), the CEA binding site binds to the same site as a Class I, II or III anti-CEA antibody. The CEA binding site binds to the same site as a Class III anti-CEA antibody. (II) is bivalent and trivalent. One arm of (II) is a Class III anti-CEA MAb that targets CD66e and another arm of (II) is from another anti-CEA cross-reactive antibody that targets CD66a-d. The binding sites are scFv or Fab regions. (II) is a bispecific, trivalent protein comprising one arm reactive with NCA50/90 and two arms reactive with only CEA. (II) is a bispecific protein comprising two arms that bind to NCA50/90. (II) is a diabody comprising one arm that binds to NCA50/90 and a second arm that binds to a Class III epitope of CEA. The NCA-50/90 arm is obtained from an hMN-3 antibody and the second arm that binds to a Class III epitope of CEA is obtained from hMN-14. (II) lacks an Fc-domain to prevent activation of cytokine release from granulocytes or which has an Fc-domain that has been modified to prevent complement fixation and ADCC. (II) is a triabody comprising one hMN-3 arm and two hMN14 arms or one hMN-15 arm and two hMN14 arms. (II) comprises at least one hMN-14 arm and at least one MN-6 arm. (II) further comprises an Fc-domain to enable complement fixation and activation of ADCC, or a therapeutic agent such as cytokine e.g., interferon, a colony-stimulating factor, or an interleukin. The colony-stimulating factor is GM-CSF or G-CSF.

ACTIVITY - Cytostatic.

MECHANISM OF ACTION - Antibody therapy; Stimulator of antibody-dependent cell-mediated cytotoxicity; Stimulator of complement-mediated lysis; Inhibitor of cell growth; Inhibitor of cell cycle progression; Stimulator of apoptosis; Inhibitor of angiogenesis. To detect the effect of naked hMN-14 CEA MAb and CPT-11 in an advanced cancer model, the following test was done. The hMN-14 was given to mice at a dose of 100 approximately mg/day over 14 days an then 2 times/week after it, starting on day 0 after tumor implantation.

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      CPT-11 was given at 60 microg/day over 5 days. No
      effect of hMN-14 by itself is apparent under these conditions, and only a
      modest effect of CPT-11 was observed. HMN-14
      increases the effect of CPT-11, as seen by comparing
      the CPT-11 median survival of 63 days against
      combination therapy median survival of 77 days. Combination therapy with
      hMN-14 CEA MAb and CPT-11 significantly prolongs
      survival of an animal with advanced human colonic tumor metastasis.
           USE - (M1) is useful for treating non-medullary or medullary thyroid
      carcinoma (claimed).
           ADMINISTRATION - 100-600 (preferably 300-400) milligrams protein per
      dose per injection of MN-14 antibody is
      administered by parenteral or subcutaneous route.
           EXAMPLE - No suitable example given. (122 pages)


=> d his

     (FILE 'HOME' ENTERED AT 15:28:59 ON 11 OCT 2006)

     FILE 'CAPLUS, BIOENG, BIOTECHNO, BIOTECHDS, ESBIOBASE' ENTERED AT
     15:29:24 ON 11 OCT 2006
L1          112 S (MN-14 AND ANTIBODY)
L2            7 S L1 AND (CYTOTOXIC AGENT)
L3            5 DUPLICATE REMOVE L2 (2 DUPLICATES REMOVED)
L4            3 S L2 AND CPT-11

=> s L1 and CPT-11
L5            5 L1 AND CPT-11

=> duplicate remove l5
DUPLICATE PREFERENCE IS 'CAPLUS, BIOTECHDS'
KEEP DUPLICATES FROM MORE THAN ONE FILE?  Y/(N):n
PROCESSING COMPLETED FOR L5
L6            4 DUPLICATE REMOVE L5 (1 DUPLICATE REMOVED)

=> d l6 bib abs 1-4

L6    ANSWER 1 OF 4  BIOTECHDS COPYRIGHT 2006 THE THOMSON CORP. on STN
AN    2005-24154  BIOTECHDS
TI    Conjugate useful as primary therapeutic agent for treating diseases e.g.,
      infectious disease and autoimmune disease, comprises one or more moieties
      having ribonucleolytic activity, and one or more folate receptor ligands;
         recombinant RNA-ase conjugate construction for use in disease
         diagnosis, RNA interference and gene therapy
AU    HANSEN H J; MCBRIDE W J; GOLDENBERG D M; ROSSI E A; CHANG C K
PA    IMMUNOMEDICS INC
PI    WO 2005069994 4 Aug 2005
AI    WO 2005-US2193 24 Jan 2005
PRAI  US 2004-538396 22 Jan 2004; US 2004-538396 22 Jan 2004
DT    Patent
LA    English
OS    WPI: 2005-564084 [57]
AN    2005-24154  BIOTECHDS
AB    DERWENT ABSTRACT:
      NOVELTY - A conjugate (I) comprises moieties having ribonucleolytic
      activity, and folate receptor ligands.
           DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for: (1)
      a complex (II) comprising moieties having ribonucleolytic activity
      conjugated to histidine tags, folate receptor ligands conjugated to
      nitrilolotriacetic acid residues, and nickel cations; and (2) treating
      and/or diagnosing a disease, comprising: (a) administering a binding
      molecule, having one arm that binds a targeted tissue and another arm
      that binds a targetable construct; (b) optionally, a clearing composition
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and allowing the composition to clear non-localized binding molecules from circulation, and (c) administering a targetable construct comprising C1.

BIOTECHNOLOGY - Preferred Conjugate: In (I), the one or more moieties comprise a recombinant RNase molecule, preferably onconase and most preferably rapLR1. The one or more moieties have pyroglutamate as an N-terminal residue. The one or more folate receptor ligands are folic acid, methotrexate or folate analog that binds to the folate receptor. The one or more folate receptor ligands are conjugated to the one or more moieties by a linker that comprises diisocyanate, diisothiocyanate, carbodiimide, bis(hydroxysuccinimide)ester, maleimide- hydroxysuccinimide ester, glutaraldehyde or their combinations. The one or more folate receptor ligands are conjugated to the one or more moieties at one or more lysine, histidine or cysteine residues. Preferred Complex: (II) further comprises a peptide that includes one or more molecules chosen from antigenic molecules, haptens, hard acid chelators and soft acid chelators, where the one or more folate receptor ligands and the one or more nitrilolotriacetic acid residues are conjugated to the peptide. (II) further comprises one or more binding molecules, where the one or more binding molecules include one or more arms that specifically bind a targeted tissue and one or more arms that specifically bind the peptide. Preferred Kit: K1 further comprises an implement for administering the therapeutic agent, one or more additional therapeutic agents or diagnostic agents.

ACTIVITY - Antibacterial; Fungicide; Antianemic; Antimalarial; Antimicrobial; Cytostatic; Cardiovascular-Gen.; Cardiant; Vasotropic; Thrombolytic; Antiparasitic; Virucide; Protozoacide; Anti-HIV; Antiinflammatory; Hepatotropic; Immunosuppressive; Hemostatic; Muscular-Gen.; Neuroprotective; Dermatological; Nephrotropic; Antirheumatic; Antipyretic; Antidiabetic; Antiarthritic; Antiulcer; Gastrointestinal-Gen.; Thyromimetic; Antiallergic; Antipsoriatic. No biological data is given.

MECHANISM OF ACTION - None given.

USE - C1 is useful for treating a disease, by administering C1 as a primary therapeutic agent, and optionally an additional therapeutic agent or a diagnostic agent. The additional agent is a binding molecule, drug, prodrug, toxin, enzyme, enzyme-inhibitor, nuclease, immunomodulator, cytokine, oligonucleotide, chelator, boron compound, photoactive agent, radionuclide, anti-angiogenic agent, dye, radioopaque material, contrast agent, fluorescent compound, and/or enhancing agent. The oligonucleotide is anti-sense or interference RNA. The binding molecule is multivalent, multispecific or bi-specific antibody. The antibody comprises MAb 679, MAb 734, MAb Mu-9, and/or MN-14.
When the disease is a malignant disease, the binding molecule specifically binds an antigen chosen from carcinoembryonic antigen, tenascin, epidermal growth factor receptor, platelet derived growth factor receptor, fibroblast growth factor receptors, vascular endothelial growth factor receptors, gangliosides, and/or HER2/neu receptors. When the disease is a cardiovascular disease, then the binding molecule is specific for granulocytes, lymphocytes, monocytes, fibrin or their mixture. The cardiovascular disease includes myocardial infarction, ischemic heart disease, artherosclerotic plaques, fibrin clots, and/or embolism. The infectious disease is caused by e.g. Microsporum, Trichophyton, Epidermophyton, Sporothrix schenckii, Cryptococcus neoformans, Candida albicans, HIV, herpes virus, cytomegalovirus, Anthrax bacillus, Streptococcus agalactiae, Legionella pneumophila, Streptococcus pyogenes, Escherichia coli, Pneumococcus, Hemophilus influenzae B, Treponema pallidum, Lyme disease spirochetes, Pseudomonas aeruginosa, Mycobacterium leprae, Brucella abortus, Tetanus, helminth, malaria parasite, Mycoplasma arthritidis, and/or M.pneumoniae. The autoimmune disease is e.g. idiopathic thrombocytopenic purpura, dermatomyositis, Sydenham's chorea, myasthenia gravis, systemic lupus erythematosus, lupus nephritis, rheumatic fever, diabetes mellitus, Takayasu's arteritis, Addison's disease, rheumatoid arthritis, multiple sclerosis, sarcoidosis,

ulcerative colitis, IgA nephropathy, polyarteritis nodosa, ankylosing spondylitis, Goodpasture's syndrome, thromboangitisubiterans, Sjogren's syndrome, primary biliary cirrhosis, Hashimoto's thyroiditis, thyrotoxicosis, scleroderma, chronic active hepatitis, polychondritis, pamphigus vulgaris, Wegener's granulomatosis, membranous nephropathy, amyotrophic lateral sclerosis, tabes dorsalis, giant cell arteritis/polymyalgia, pernicious anemia, rapidly progressive glomerulonephritis, psoriasis, and/or fibrosing alveolitis. When the disease, is a metabolic or neurological disease, then the binding molecule specifically binds an amyloid deposit. The drug includes aplidin, azaribine, anastrozole, azacytidine, bleomycin, bortezomib, bryostatin-1, busulfan, camptothecin, 10-hydroxycamptothecin, carmustine, celebrex, chlorambucil, cisplatin, irinotecan (CPT-11), SN-38, carboplatin, doxorubicin, etoposide phosphate, floxuridine (FUdR), L-asparaginase, leucovorin, lomustine, tamoxifen, taxol, testosterone propionate, thalidomide, vinorelbine, vincristine, ricin, abrin, ribonuclease, onconase, rapLR1, DNaseI, Staphylococcal enterotoxin-A, pokeweed antiviral protein, gelonin, diphtheria toxin, Pseudomonas exotoxin, and/or Pseudomonas endotoxin. The radionuclide is 18F, 32P, 33P, 45Ti, 47Sc, 52Fe, 59Fe, 62Cu, 64Cu, 67Cu, 67Ga, 68Ga, 75Se, 77As, 86Y, 89Sr, 89Zr, 90Y, 94Tc, 99Mo, 99mTc, 105Pd, 105Rh, 111Ag, 111In, 123I, 124I, 125I, 131I, 142Pr, 143Pr, 149Pm, 153Sm, 154-158Gd, 161Tb, 166Dy, 166Ho, 169Er, 175Lu, 177Lu, 186Re, 189Re, 194Ir, 198Au, 199Au, 211At, 212Pb, 212Bi, 212Pb, 213Bi, 223Ra, and/or 225Ac. It is used for performing positron-emission tomography (PET). The enzyme is carboxylesterases, glucuronidases, carboxypeptidases, beta-lactamases, phosphatases, nucleases, proteases, and/or lipases. The immunomodulator or cytokine comprises IL-1, -2, -3, -6, -10, -12, -18, -21, interferon-alpha, -beta, -gamma, granulocyte colony stimulating factor (G-CSF) and/or granulocyte macrophage (GM)-CSF. The anti-angiogenic agent is angiostatin, endostatin, baculostatin, canstatin, and/or maspin. The method also involves administering a diagnostic agent, preferably photosensitizer, preferably benzoporphyrin monoacid ring A (BDP-MA), tin etiopurpurin (SnET2), sulfonated aluminum phthalocyanine (AlSPc) and lutetium texaphyrin (Lutex). The diagnostic agent comprises image enhancing agents comprising Gd ions, Ln ions, Mn ions, Fe, Cr, Cu, Co, Ni, F, Dy, Re, Eu, Tb, Ho, and/or Nd. The diagnostic agent comprises radiopaque materials or contrast agents for X-ray or computed tomography (CT), preferably barium, diatrizoate, ethiodized oil, gallium citrate, iocarmic acid, iocetamic acid, iodamide, iodipamide, iodoxamic acid, iogulamide, iohexol, iopamidol, iopanoic acid, ioprocemic acid, iosefamic acid, ioseric acid, iosulamide meglumine, iosemetic acid, iotasul, iotetric acid, iothalamic acid, iotroxic acid, ioxaglic acid, ioxotrizoic acid, ipodate, meglumine, metrizamide, metrizoate, propyliodone, and/or hallous chloride. The diagnostic agent comprises contrast agents for performing an ultrasound imaging. The liposome is gas-filled. The method further involves administering Zn, Al, Ga, Lu, Pd, B, Gd, Ur, Mn, Fe, Cr, Cu, Co, Ni, Dy, Re, Eu, Tb, Ho, Nd, Cr3+, Mn2+, Fe2+, Fe3+, Co2+, Ni2+, Cu2+, Nd3+, Sm3+, Yb3+, Gd3+, V2+, Tb3+, Dy3+, Ho3+, and/or Er3+. (All claimed.)

ADMINISTRATION - (I) or C1 is administered by parenteral route such as intravenous route. The dosage of (I) is 0.01-300 mg, preferably 0.1-10 mg/patient per day.

EXAMPLE - Preparation of onconase-folate conjugates was carried out as follows. Onconase-folate conjugates were prepared as described in Leamon, et al., (1993) J.Biol. Chemical 267, 24966-71. The folate was dissolved in anhydrous dimethyl sulfoxide and activated with 5-fold molar excess of 1-ethyl-3-(3-dimethylamineopropyl) and carbodiimide for 1 hour at 23degreesC. Onconase was dissolved in disodium hydrogen phosphate (in M) (0.1) and boric acid (0.1), pH 8.5. A 5-8 fold molar excess of the activated folate was then added to the onconase solution, and the conjugation reaction was allowed to proceed at 23degreesC for 30 minutes. Then the unreacted material was separated from the conjugate using a Sephadex G-25 column equilibrated in phosphate-buffered saline, pH 7.4.

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      Samples were filtered through 0.2 microns syringe filters and then
      assayed for protein content using standard methods such as a
      bicinchoninic acid assay (BCA) kit. Peak fractions were pooled and
      analyzed by sodium dodecyl sulfate-polyacrylamide gel electrophoresis
      (SDS-PAGE) to determine the amount of free ligand and recombinant
      onconase in the conjugates.(40 pages)

L6   ANSWER 2 OF 4  CAPLUS  COPYRIGHT 2006 ACS on STN  DUPLICATE 1
AN   2004:331925  CAPLUS
DN   140:355848
TI   humanized or chimeric derivatives of murine monoclonal anti-CEA
     antibody MN-14 and conjugates for cancer
     therapy
IN   Goldenberg, David M.; Hansen, Hans J.
PA   Immunomedics, Inc., USA
SO   PCT Int. Appl., 121 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 2
     PATENT NO.          KIND    DATE        APPLICATION NO.        DATE
     ---------------     ----    --------    --------------------   --------
PI   WO 2004032857        A2     20040422    WO 2003-US31801        20031008
     WO 2004032857        C1     20050407
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE,
             GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK,
             LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ,
             OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM,
             TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
             KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
             FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,
             BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
     WO 2004032962        A1     20040422    WO 2002-US32307        20021011
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
             GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
             LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
             PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,
             UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
             KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
             FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF,
             CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
     CA 2501616           AA     20040422    CA 2003-2501616        20031008
     AU 2003282752        A1     20040504    AU 2003-282752         20031008
     EP 1572131           A2     20050914    EP 2003-774636         20031008
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK
     JP 2006521286        T2     20060921    JP 2005-501118         20031008
PRAI US 2002-416531P      P      20021008
     WO 2002-US32307      A      20021011
     US 2003-467161P      P      20030502
     WO 2003-US31801      W      20031008
AB   The present invention provides a composition comprising naked humanized or
     chimeric murine monoclonal antibody MN-14
     and a therapeutic agent, which is useful for treatment of CEA expressing
     cancers and other diseases, and methods of use in treatment using this
     composition

L6    ANSWER 3 OF 4  BIOTECHDS COPYRIGHT 2006 THE THOMSON CORP. on STN
AN    2004-17817  BIOTECHDS
TI    Immunoconjugate useful for treating autoimmune disease, comprises
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targeting moiety, chemotherapeutic moiety, linker that binds to targeting moiety through thiol group and to chemotherapeutic moiety through intracellular-cleavable moiety;

an immunoconjugate comprising e.g. monoclonal antibody and humanized antibody and a chemotherapeutic moiety useful for disease therapy

AU GOVINDAN V S
PA IMMUNOMEDICS INC; MCCALL J D
PI WO 2004054622 1 Jul 2004
AI WO 2003-GB5454 15 Dec 2003
PRAI US 2002-433017 13 Dec 2002; US 2002-433017 13 Dec 2002
DT Patent
LA English
OS WPI: 2004-500142 [47]
AN 2004-17817 BIOTECHDS
AB DERWENT ABSTRACT:

NOVELTY - An immunoconjugate (I) comprising targeting moiety, chemotherapeutic moiety, and linker binding to targeting moiety through thiol group, and to chemotherapeutic moiety through intracellular-cleavable moiety other than hydrazone, is new.

BIOTECHNOLOGY - Preferred Immunoconjugate: In (I), the intracellular-cleavable moiety is cleavable by intracellular esterases. The intracellular-cleavable moiety is an ester moiety formed from alpha-carboxylic acid of an amino acid. The intracellular-cleavable moiety comprises a peptide bond cleavable by intracellular enzymes. The intracellular-cleavable moiety comprises an ether bond, susceptible to cleavage under the acidic pH of intracellular compartments. The ether bond is formed between the chemotherapeutic agent and intracellular-cleavable moiety. The intracellular-cleavable moiety comprises tetrahydropyran moiety, tetrahydrofuran moiety or an orthoester moiety. The linker comprises a thiol-reactive group which links to thiol groups of targeting moiety. The thiol-reactive group is a maleimide or vinylsulfone, which links to thiol groups of targeting moiety. The linker comprises a thiol group that reacts with a maleimide residue at a lysine side chain of targeting moiety. (I) further comprises a water-solubilizing moiety between the chemotherapeutic moiety and the targeting moiety. The water-solubilizing moiety is an aminopolycarboxylate chosen from diethylenetriamine-pentaacetic acid (DTPA), ethylenediaminetetraacetic acid (EDTA), ((2-(Bis-carboxymethyl-amino)-ethyl)-(2-((2-(bis-carboxymethyl-amino)-ethyl)-carboxymethyl-amino)-ethyl)-amino)-acetic acid (TTHA), benzyl-DTPA, (4,7,10-Tris-carboxymethyl-1,4,7,10-tetraaza-cyclododec-1-yl)-acetic acid (DOTA), benzyl-DOTA, (4,7-Bis-carboxymethyl-(1,4,7)triazonan-1-yl)-acetic acid (NOTA), benzyl-NOTA, 10-Carboxymethyl-1,4,7,10-tetraaza-cyclotetradecane-1,4,7-tricarboxylic acid (TETA) and N,N'-dialkyl substituted piperazine. The chemotherapeutic moiety is chosen from doxorubicin (DOX), epirubicin, morpholino-DOX, cyanomorpholino-DOX, 2-pyrrolino-doxorubicin(2-PDOX), CPT, CPT-11, SN-38, topotecan, taxanes, geldanamycin, ansamycins, and epothilones. The targeting moiety is an antibody or an antigen-binding fragment. The antibody is a monoclonal antibody (mAb) that is multivalent and/or multispecific. The targeting moiety is a murine, chimeric, humanized, or human monoclonal antibody. The antibody is in intact, fragment (Fab, Fab', F(ab)2, F(ab')2), or sub-fragment (single-chain constructs) form. The targeting moiety is a monoclonal antibody that is reactive with an antigen or epitope of an antigen expressed on a cancer cell (e.g., hematopoietic tumor, carcinoma, sarcoma, melanoma or a glial tumor) or malignant cell. The targeting moiety is a monoclonal antibody that binds to B-cell lineage antigen, T-cell antigen, myeloid lineage antigen and HLA-DR antigen. The targeting moiety is a monoclonal antibody that binds to an antigen such as CD74, CD22, epithelial glycoprotein-1, MUC1, carcinoembryonic antigen (CEA or CD66e), colon-specific antigen-p, alpha-fetoprotein, CC49 or prostate-specific membrane antigen.

Optionally, targeting moiety is a bispecific and/or bivalent antibody construct comprising one or more antibodies chosen from LL1, LL2, hA20, IF5, L243, RS7, PAM-4, MN-14, Mu-9, AFP-31, G250, J591, CC49 and Immu 31. The targeting moiety links to one or more chemotherapeutic moiety. The targeting moiety links to 7-12 chemotherapeutic moieties. The linker comprises a peptide comprising a thiol-reactive moiety at its N-terminus, for linkage to the targeting moiety and one or more side chain amino groups for linkage to one or more chemotherapeutic moiety. (I) is in a form suitable for parenteral administration. In (I), the linker comprises a functional group at N-terminus, water-solubilizing moiety at C-terminus, and one or more internal basic amino acids with side chains available for attachment to chemotherapeutic moiety. The linker has a formula 1. R = undefined.

ACTIVITY - Cytostatic; Immunosuppressive; Hemostatic; Neuroprotective; Muscular-Gen.; Antiinflammatory; Dermatological; Antipyretic; Antirheumatic; Antiarthritic; Dermatological; Antidiabetic. No biological data is given.

MECHANISM OF ACTION - None given.

USE - (I) is useful for treating malignancy (e.g. malignant solid tumor or hematopoietic neoplasm), autoimmune disease (e.g. class III autoimmune disease), infection, or infectious lesion in subject. The class (III) autoimmune disease is chosen from immune-mediated thrombocytopenias, dermatomyositis, Sjogren's syndrome, multiple sclerosis, Sydenham's chorea, myasthenia gravis, systemic lupus erythematosus, lupus nephritis, rheumatic fever, rheumatoid arthritis, polyglandular syndromes, bullous pemphigoid, diabetes mellitus, etc. (I) targets an antigen or epitope or iron-siderophore chelate receptor on a pathogen (e.g. bacterium, fungus, virus, rickettsia, mycoplasma and protozoa) associated with infection or infectious lesion. Preferably, the pathogen includes any one of the following: Streptococcus agalactiae, Neisseria meningitides, Pneumococcus, Hemophilis influenza B, Treponema pallidum, Lyme disease spirochetes, Pseudomonas aeruginosa, Mycobacterium leprae, Brucella abortus, Mycobacterium tuberculosis, rabies virus, influenza virus. (All claimed.)

ADMINISTRATION - (I) is administered by parenteral route (claimed).

ADVANTAGE - (I) exhibits improved ability to target various cancer cells due to the presence of targeting moiety and therapeutic moiety. The efficacy of (I) is increased since targeting and therapeutic moieties are coupled by an acid cleavable linkage.

EXAMPLE - No relevant example is given.(41 pages)

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L6   ANSWER 4 OF 4  CAPLUS  COPYRIGHT 2006 ACS on STN
AN   2003:320021  CAPLUS
DN   138:336427
TI   Direct targeting binding multivalent monospecific proteins of human
IN   Rossi, Edmund; Chang, Chien-Hsing Ken; Goldenberg, David M.
PA   IBC Pharmaceuticals, USA; Immunomedics Inc.
SO   PCT Int. Appl., 62 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 2
     PATENT NO.          KIND   DATE       APPLICATION NO.        DATE
     ---------------     ----   --------   --------------------   --------
PI   WO 2003033654        A2    20030424   WO 2002-US32718        20021015
     WO 2003033654        A3    20031113
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
             GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
             LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
             PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,
             UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
             KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
             FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF,
             CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
     CA 2463672          AA    20030424   CA 2002-2463672        20021015
     US 2003148409       A1    20030807   US 2002-270073         20021015
     EP 1448780          A2    20040825   EP 2002-782156         20021015
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK
     JP 2005507659       T2    20050324   JP 2003-536384         20021015
     CN 1604966          A     20050406   CN 2002-825068         20021015
     BR 2002013303       A     20050607   BR 2002-13303          20021015
PRAI US 2001-328835P     P     20011015
     US 2001-341881P     P     20011221
     US 2002-345641P     P     20020108
     US 2002-404919P     P     20020822
     WO 2002-US32718     W     20021015
AB   The present invention relates to multivalent, monospecific binding
     proteins.  These binding proteins comprise two or more binding sites,
     where each binding site specifically binds to the same type of target
     cell, and preferably with the same antigen on such a target cell.  The
     present invention further relates to compns. of monospecific diabodies,
     triabodies, and tetrabodies, and to recombinant vectors useful for the
     expression of these functional binding proteins in a microbial host.  Also
     provided are methods of using invention compns. in the treatment and/or
     diagnosis of tumors.


=> s anti-CEA antibody
L7          536 ANTI-CEA ANTIBODY

=> s class III and L7
L8            6 CLASS III AND L7

=> duplicate remove l8
DUPLICATE PREFERENCE IS 'BIOTECHNO, BIOTECHDS'
KEEP DUPLICATES FROM MORE THAN ONE FILE? Y/(N):n
PROCESSING COMPLETED FOR L8
L9             6 DUPLICATE REMOVE L8 (0 DUPLICATES REMOVED)

=> d l9 bib abs 1-6

L9    ANSWER 1 OF 6  BIOTECHDS COPYRIGHT 2006 THE THOMSON CORP. on STN
AN    2005-09145  BIOTECHDS
TI    New immunological reagent useful for treating e.g. tumor, cancer,
      infectious disease, autoimmune disease, cardiovascular disease;
         the use of a monoclonal antibody, humanized antibody and multispecific
         antibody in a pharmaceutical composition for disease diagnosis and
         immunotherapy
AU    MCBRIDE W J; GOLDENBERG D M
PA    IMMUNOMEDICS INC
PI    US 2005025709 3 Feb 2005
AI    US 2004-866180 14 Jun 2004
PRAI  US 2004-866180 14 Jun 2004; US 2003-478403 13 Jun 2003
DT    Patent
LA    English
OS    WPI: 2005-161238 [17]
AN    2005-09145  BIOTECHDS
AB    DERWENT ABSTRACT:
      NOVELTY - Immunological reagent is new.
           DETAILED DESCRIPTION - Immunological reagent of formula
      X-R1-D-T1(A)-R2(Z)-D-T1(B')-R3(Y)-NR4R5 or R1(X)-D-T1(A)-R2(Z)-D-T1(B')-
      R3(Y)-NR4R5 is new. T1 = Dpr, Orn or Lys; X = hard acid cation chelator,
      a soft acid cation chelator or Ac-; R1 - R3 = covalent bond or at least
      one D-amino acid; Y or Z = hard acid cation chelator, soft acid cation
      chelator or absent; A and B' = haptens or hard acid cation chelators; R4
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and R5 = hard acid cation chelators, soft acid cation chelators, enzymes, therapeutic agents, diagnostic agents or H. INDEPENDENT CLAIMS are included for: (1) diagnosing (m1) and/or treating a disease or a condition leading to the disease involving administering a targetable construct (c1) comprising the immunological agent to a subject having the disease or the condition, where the construct containing at least one diagnostic or therapeutic cation and/or at least one chelated or chemically bound therapeutic agent, diagnostic agent or enzymes; and administering a multispecific antibody or antibody fragments to the subjects, where the multispecific antibody or antibody fragment has at least one arm which binds to a targeted tissue and at least one other arm which binds the construct; (2) detecting (m2), identifying or treating a target cell, tissue or pathogen in a subject involving administering a targetable construct (c2) comprising the immunological agent; and administering a multispecific antibody or antibody fragment to the subject, where the multispecific antibody or antibody fragment comprises at least one arm which binds a target cell, tissue or pathogen and at least one other arm which binds (c2); and (3) a kit for treating or identifying diseased tissues in a subject comprising a targetable construct, and a multispecific antibody or antibody fragment having at least one arm which binds a targeted tissue and at least one other arm which binds the targetable construct.

BIOTECHNOLOGY - Preferred Components: The targeted tissue is a tumor. The tumor produces or is associated with 40 antigens as given in specification e.g. colon-specific antigen-p (CSAp). At least one arm which binds the targeted tissue is a monoclonal antibody or a fragment of a monoclonal antibody. At least one other arm binds the targeted construct is a monoclonal antibody or a fragment of a monoclonal antibody. The targeted tissue or construct is a human, chimeric or humanized antibody or a fragment of a human, chimeric or humanized antibody. The multispecific antibody or antibody fragment further comprises a 41 therapeutic nuclide as given specification, e.g. 177Lu. The multispecific antibody comprises the Fv of MAb Mu-9 and the Fv of MAb 679. Mu-9 and/or 679 are chimerized or humanized (preferably human Mu9 and 679). The multispecific antibody comprises at least one of CDRs of Mu-9 or CDRs of 679. The multispecific antibody is a fusion protein. The multispecific antibody comprises the Fv of MAb MN-14 and the Fv of MAb 679. MN-14 and/or 679 are chimerized or humanized (preferably human MN-14 or 679). The multispecific antibody comprises at least one of CDRs of MN-14 or at least one of CDRs of 679. The multispecific antibody is a fusion protein. The fusion protein is trivalent and incorporates the Fv of an antibody reactive with CSAp. The multispecific antibody incorporates a Class-III anti-CEA
antibody and the Fv of 679. The target comprises a molecule produced by or associated with the target cell, tissue or pathogen. The target tissue is a diseased tissue. The diseased tissue is identified intraoperatively, endoscopically or intravascularly. The multispecific antibody or antibody fragment is bispecific.

ACTIVITY - Cytostatic; Virucide; Antibacterial; Antimicrobial; Antiinflammatory; Immunosuppressive; Hemostatic; Dermatological; Muscular-Gen.; Neuroprotective; Antipyretic; Antidiabetic; Nephrotropic; Anabolic; Hypertensive; Antirheumatic; Antiarthritic; Neuroprotective; Antiulcer; Hepatotropic; Thyromimetic; Antiallergic; Vasotropic; Antianemic; Antipsoriatic; Cardiovascular-Gen.; Cardiant; Antiarteriosclerotic; Thrombolytic; Nootropic.

MECHANISM OF ACTION - None given.

USE - In a targetable construct for diagnosing and/or treating tumor, cancer (preferably leukemias, lymphomas, sarcomas, melanomas, carcinomas, gliomas, skin cancers, B-cell malignancy, B-cell lymphoma, chronic lymphatic leukemia, non-Hodgkin's lymphoma, acute lymphatic leukemias, multiple myeloma or cancer is esophageal, gastric, colonic, rectal, pancreatic, lung, breast, ovarian, urinary bladder, endometrial, cervical, testicular, renal, adrenal or liver cancer), infectious disease caused by pathogens, an inflammatory disease, autoimmune disease (e.g.

acute idiopathic thrombpcytopenic purpura, chronic idiopathic thrombocytopenia purpura, dermatomyositis, Sydenham's chorea, myasthenia gravis, systemic lupus erythematosus, lupus nephritis, rheumatic fever, polyglandular syndrome, bullous pemphigoid, diabetic mellitus, Henoch-Schonlein purpura, post-streptococcalnephritis, erythema nodosurn, Takayasu's arteritis, Addison's disease, rheumatoid arthritis, multiple sclerosis, sarcoidosis, ulcerative colitis, erythema multiforme, IgA nephropathy, polyarteritis nodosa, ankylosing spondylitis, Goodpasture's syndrome, thromboangitisubiterans, Sjogren's syndrome, primary biliary cirrhosis, Hashimoto's thyroiditis, thyrotoxicosis, scleroderma, chronic active hepatitis, polymyositis/dermatomyositis, polychondritis, pamphigus vulgaris, Wegener's granulomatosis, membranous nephropathy, amyotrophic lateral sclerosis, tabes dorsalis, giant cell arteritis/polymyalgia, pernicious anemia, rapidly progressive glomerulonephritis, psoriasis and fibrosing alveolitis), cardiovascular disease (e.g. myocardial infarction, ischemic heart disease, atherosclerosis plaques, clots and emboli), metabolic disease (e.g. amyloidosis) and neurological disease (e.g. Alzheimer's disease) in subject (preferably humans, primates, equines, canines or felines (claimed). In radioimmunotherapy (RAIT) and radioimmunodetection (RAID) and MRI.

ADVANTAGE - The immunological agent binds to a targetable diagnostic or therapeutic conjugate and a flexible system which accommodates different diagnostic and therapeutic agents without alteration to the bi-specific or multi-specific antibodies.

EXAMPLE - Sieber Amide resin was reacted with Fmoc-D-Lys(Aloc)-OH, Fmoc-D-Asp(But)-OH, Fmoc-D-Lys(Aloc)-OH and Fmoc-D-Asp(But)-OH to give the corresponding protected tetra-peptide, which was reacted with DOTA-tris(tBu)ester, followed by removal of the Aloc side chain on D-lysines using Pd(P(Ph)3)4 to give DOTA(tris t-Bu)-D-Asp(tBu)-D-Lys-D-Asp(tBu)-D-Lys-NH-resin, which was reacted with trityl HSG ligands in presence of BOP/HBTU to form DOTA-D-Asp(tBu)-D-Lys(HSG)-D-Asp(tBu)-D-Lys(HSG)-NH-resin. The peptide was cleaved from the resin and the protecting groups were removed to give DOTA-D-Asp-D-Lys(HSG)-D-Asp-D-Lys(HSG)-NH2 (IMP 271). (62 pages)

L9 ANSWER 2 OF 6 BIOTECHDS COPYRIGHT 2006 THE THOMSON CORP. on STN
AN 2005-20559 BIOTECHDS
TI Inducing an immune response against a tumor or a disease caused by an infectious agent, comprises administering a vaccine comprising an antibody component that binds with a tumor antigen and an anti-idiotype antibody component;
a recombinant vaccine comprising a monoclonal antibody specific for a tumor-associated antigen and nucleic acid vaccine useful for a cancer gene therapy application
AU HANSEN H J
PA IMMUNOMEDICS INC
PI CA 2448831 25 May 2005
AI CA 2003-2448831 25 Nov 2003
PRAI CA 2003-2448831 25 Nov 2003; CA 2003-2448831 25 Nov 2003
DT Patent
LA English
OS WPI: 2005-459159 [47]
AN 2005-20559 BIOTECHDS
AB DERWENT ABSTRACT:
NOVELTY - Inducing (M1) humoral and cellular immune responses in a mammal against a tumor that expresses TAA or against a disease caused by an infectious agent by administering a vaccine comprising an antibody component that binds with the TAA or with an antigen associated with the infectious agent, and administering a second vaccine comprising an anti-idiotype antibody component to the mammal.

DETAILED DESCRIPTION - Inducing (M1) humoral and cellular immune responses in a mammal against a tumor that expresses a tumor associated antigen (TAA) or against a disease caused by an infectious agent, comprises: (a) administering a first vaccine to the mammal, where the

first vaccine comprises an antibody component that binds with the TAA or with an antigen associated with the infectious agent, and antibody component is conjugated with a soluble immunogenic carrier protein and administering a second vaccine to the mammal, where the second vaccine comprises an anti-idiotype antibody component that mimics an epitope of the TAA or the infectious agent, and the anti-idiotype antibody component is conjugated with a soluble immunogenic carrier protein; (b) administering a vaccine to the mammal, the vaccine comprises an antibody component that binds with the TAA or with an antigen associated with the infectious agent, and the antibody component in conjugated with a soluble immunogenic carrier protein and administering an antibody or its antigen-binding fragment, where the antibody or its fragment is not conjugated with a soluble immunogenic carrier protein, and the antibody or its fragment binds with the TAA or with an antigen associated with the infectious agent; (c) obtaining T cells from the patient, introducing an expression vector into the T cells to obtain transfected T cells, where expression vector comprises a DNA molecule encoding either a chimeric immunoglobulin/T cell receptor or a chimeric immunoglobulin/CD3 protein, and the immunoglobulin-encoding portion of the DNA molecule encodes the variable region of an antibody that binds with the TAA or with an antigen associated with the infectious agent, stimulating the proliferation of the transfected T cells to obtain an increased mass of transfected T cells and returning the increased mass of transfected T cells to the patient; or (d) administering a first vaccine, administering an antibody or its antigen-binding fragment, which is not conjugated with a soluble immunogenic carrier protein, and which binds with the TAA or with an antigen associated with the infectious agent and administering a second vaccine to the mammal. INDEPENDENT CLAIMS are also included for the following: (1) a vaccine (V1) for treating a patient having a tumor that expresses carcinoembryonic antigen (CEA), comprising a carrier and an anti-CEA antibody component which is
conjugated with a soluble immunogenic carrier protein, or anti-idiotype antibody component which is conjugated with a soluble immunogenic carrier protein, and mimics an epitope of CEA; and (2) treating (M2) a patient having a tumor that expresses CEA, comprising administering a bispecific antibody to the patient, where the bispecific antibody comprises a group that binds with a CD3 protein and a group that binds with CEA, and the CEA-binding group is derived from a class III
anti-CEA antibody.

BIOTECHNOLOGY - Preferred Method: The antibody component of (M1a) includes a murine monoclonal antibody, humanized antibody derived from murine monoclonal antibody, human monoclonal antibody and its antibody fragments. The antibody fragment is chosen from F(ab')2, F(ab)2, Fab', Fab, Fv, sFv and minimal recognition unit. The anti-idiotype antibody component includes a polyclonal antibody, murine monoclonal antibody, humanized antibody derived from murine monoclonal antibody, human monoclonal antibody, subhuman primate antibody or its antibody fragment. (M1a) Further involves administering interleukin-2 and/or interferon-gamma prior to and during the administration of the second vaccine. The antibody or its fragment of (M1b) is conjugated with biotin. (M1b) Further involves administering avidin to decrease circulating levels of the biotinylated antibody or its fragment, administering a vaccine for a second time and administering interleukin-2 and/or interferon-gamma prior to and during the second administration of the vaccine. (M1c) Further involves administering one or more cytokine chosen from interferon-gamma and interleukin-2, after returning the transfected T cells to the patient and administering a vaccine to the patient, where the vaccine comprises an anti-idiotype antibody component that binds with the immunoglobulin group of the chimeric immunoglobulin/T cell receptor or the immunoglobulin/CD3 protein, and anti-idiotype antibody component is conjugated with a soluble immunogenic carrier protein. (M1c) Further involves administering the vaccine comprising an anti-idiotype antibody component to the patient. Preferred Vaccine: The anti-
CEA antibody component of (V1) includes a murine

monoclonal class III anti-CEA antibody, humanized antibody derived from a murine monoclonal class III anti-CEA antibody, human monoclonal anti-CEA antibody or its fragment. The anti-idiotype antibody component includes a polyclonal or monoclonal antibody that binds with the variable region of a class III anti-CEA antibody, a humanized antibody derived from the monoclonal antibody, a subhuman primate antibody, a human monoclonal anti-CEA antibody or its antibody fragment.

ACTIVITY - Cytostatic; Antimicrobial.

MECHANISM OF ACTION - Vaccine (claimed). To detect the effect of (V1), a patient with Dukes C colon carcinoma was subjected to fluorouracil and levamisole adjuvant therapy. The patient was immunized subcutaneously with hMN-14 vaccine (25 mg). On day 40, the patient was immunized intravenously with hMN-14 vaccine. The tumor size was increased after 6 months. The patient was further immunized subcutaneously with WI2 vaccine (2 mg). The size of the tumor was measured. The result showed significant reduction in tumor size.

USE - (M1) Is useful for inducing humoral and cellular immune responses in a mammal against a tumor that expresses TAA or against a disease caused by an infectious agent. (C1) Or (M2) is useful for treating a patient having a tumor that expresses CEA (all claimed).

ADMINISTRATION - (V1) Is administered by subcutaneous, intramuscular or intraperitoneal route. No specific dosage detail is given. (48 pages)

L9 ANSWER 3 OF 6 BIOTECHDS COPYRIGHT 2006 THE THOMSON CORP. on STN
AN 2004-14328 BIOTECHDS
TI Treating non-medullary thyroid carcinoma or medullary thyroid carcinoma comprises administering, either concurrently or sequentially, Class III anti-CEA (carcinoembryonic antigen) monoclonal antibody or fragment and therapeutic agent(s);
humanized antibody, chimeric antibody or monoclonal antibody production for cancer therapy
AU GOLDENBERG D M; HANSEN H J
PA IMMUNOMEDICS INC
PI WO 2004032962 22 Apr 2004
AI WO 2002-US32307 11 Oct 2002
PRAI US 2002-416531 8 Oct 2002; US 2002-416531 8 Oct 2002
DT Patent
LA English
OS WPI: 2004-364813 [34]
AN 2004-14328 BIOTECHDS
AB DERWENT ABSTRACT:

NOVELTY - Treating a non-medullary thyroid carcinoma or treating medullary thyroid carcinoma involves administering to a subject, either concurrently or sequentially, a Class III anti-CEA (carcinoembryonic antigen) monoclonal antibody or its fragment and at least one therapeutic agent.

BIOTECHNOLOGY - Preferred Method: The antibody or its fragment is: (a) humanized MAb; (b) chimeric MAb; or (c) fully human MAb, where the humanized, chimeric, or fully human MAb retains substantially the Class III anti-CEA binding specificity of a murine Class III anti-CEA MAb. Preferably, the antibody or its fragment is MN-14 antibody or its fragment. The MN-14 monoclonal antibody or its fragment comprises the complementarity-determining regions (CDRs) of a murine MN-14 monoclonal antibody, where the CDRs of the light chain variable region of the MN-14 antibody comprises: (a) CDR1 Lys-Ala-Ser-Gln-Asp-Val-Gly-Thr-Ser-Val-Ala (S1); (b) CDR2 Trp-Thr-Ser-Thr-Arg-His-Thr (S2); and (c) CDR3 Gln-Gln-Tyr-Ser-Leu-Tyr-Arg-Ser (S3). The CDRs of the heavy chain variable region of (II) comprise: (a) CDR1 Thr-Tyr-Trp-Met-Ser (S4); (b) CDR2 Glu-Ile-His-Pro-Asp-Ser-Ser-Thr-Ile-Asn-Tyr-Ala-Pro-Ser-Leu-Lys-Asp (S5); and (c) CDR3 Leu-Tyr-Phe-Gly-Phe-Pro-Trp-Phe-Ala-Tyr (S6). The MN-14 monoclonal antibody reacts with CEA and is uncreative with normal cross-reactive antigen (NCA) and meconium antigen (MA), where preferably the MN-14 monoclonal antibody or its fragment, is a humanized MN-14 antibody, chimeric MN-14 antibody or fully human MN-14 antibody, or their fragments. The framework regions (FRs) of the light and heavy chain variable regions of the humanized MN-14 antibody or its fragment comprise at least one amino acid substituted from the corresponding FRs of a murine MN-14 monoclonal antibody. The humanized MN-14 antibody or its fragment comprising at least one amino acid from the corresponding FR of the murine MN-14 antibody is chosen from amino acid residue 24, 28, 30, 48, 49, 74 and 94 of the murine heavy chain variable region as given in specification. The humanized MN-14 antibody or its fragment comprises at least one amino acid from the corresponding FR of the murine MN-14 light chain variable region. The humanized MN-14 antibody or its fragment comprises the light chain variable region and the heavy chain variable region, as given in specification. The chimeric MN-14 antibody or its fragment comprises the light chain variable region and the heavy chain variable region as given in specification. The fragment is chosen from F(ab')2, Fab', Fab, Fv and scFv. The therapeutic agent is chosen from naked antibody, cytotoxic agent, drug, radionuclide, immunomodulator, photoactive therapeutic agent, immunoconjugate, hormone, or their combinations, optionally formulated in a vehicle. The combination comprises vincristine, doxorubicin, dacarbazine (DTIC) and cyclophosphamide. Optionally, the therapeutic agent is a naked antibody or an immunoconjugate, where the naked antibody or an antibody portion of the immunoconjugate comprises a humanized, chimeric, human or murine monoclonal antibody or its fragment chosen from monoclonal antibody or its fragment reactive with EGP-1, EGP-2 (e.g., 17-1A), MUC-1, MUC-2, MUC-3, MUC-4, PAM-4, KC4, TAG-72, EGFR, EGP-2, HER2/neu, BrE3, Le-Y, A3, A33, Ep-CAM, AFP, Tn, Thomson-Friedenreich antigens, tumor necrosis antigens, vascular endothelial growth factor (VEGF) or other tumor angiogenesis antigens, Ga 733, or their combination. The cytotoxic agent is a drug or a toxin, where the drug possesses the pharmaceutical property chosen from antimitotic, alkylating, antimetabolite, antiangiogenic, apoptotic, alkaloid, COX-2, and antibiotic agents and their combinations. The drug is chosen from nitrogen mustards, ethylenimine derivatives, alkyl sulfonates, nitrosoureas, triazenes, folic acid analogs, anthracyclines, taxanes, COX-2 inhibitors, pyrimidine analogs, purine analogs, antimetabolites, antibiotics, enzymes, epipodophyllotoxins, platinum coordination complexes, vinca alkaloids, substituted ureas, methyl hydrazine derivatives, adrenocortical suppressants, antagonists, endostatin, taxols, camptothecins, doxorubicins, or their analogs or combination. The alkylating agent is dacarbazine. The toxin is a microbial, plant or animal toxin chosen from ricin, abrin, alpha toxin, saporin, ribonuclease (RNase), DNase I, Staphylococcal enterotoxin-A pokeweed antiviral protein, gelonin, diphtheria toxin, Pseudomonas endotoxin. The immunomodulator is chosen from cytokine, stem cell growth factor, lymphotoxin, hematopoietic factor, colony stimulating factor (CSF), interferon (IFN), stem cell growth factor, erythropoietin, thrombopoietin and their combination. The lymphotoxin is tumor necrosis factor (TNF), the hematopoietic factor is an interleukin (IL), the colony stimulating factor is granulocyte-colony stimulating factor (G-CSF) or granulocyte macrophage-colony stimulating factor (GM-CSF), the interferon is interferons-alpha, -beta, or -gamma, and the stem cell growth factor is designated S1 factor. The immunomodulator comprises IL-1, IL-2, IL-3, IL-6, IL-10, IL-12, IL-18, interferon-gamma, TNF-alpha or their combinations. The radionuclide has an energy between 20 and 10000 keV and is chosen from 125I, 131I, 90Y, 88Y, 225Ac, 177Lu, 188Re, 186Re, and their combination. The photoactive therapeutic agent is a chromogen or dye.

ACTIVITY - Cytostatic. Tumors were propagated in female nu/nu mice at 6-8 weeks of age by subcutaneous injection of 2x108 washed TT cells (a human medullary thyroid cell line), which had been propagated in tissue culture. Treatment began 2 days after TT cell injection, hMN-14 was given daily (intraperitoneally), except Sunday at 100 microg/dose/mouse on days 2 through 11. The antibody treatment was initiated on the same day as dacarbazine (DTIC) treatment. DTIC was given on days 2, 3, and 4 at 50 and 75 microg/dose. 6 groups of mice were taken each group containing 10 mice. Group 1: untreated. Group 2: DTIC at 50 microg/dose, days 2, 3, and 4 (Wednesday, Thursday, and Friday). Group 3: DTIC at 75 microg/dose, days 2, 3, and 4. Group 4: DTIC at 50 microg/dose, days 2, 3, and 4, plus hMN-14 (100 microg/dose) days 2, 3, 4, 5, 7, 8, 9, 10, 11, 15 and 22, then every 7 days until the animal died, the tumor attained a volume of 2 cm3, or the study terminated. Group 5: DTIC at 25 microg/dose, days 2, 3, and 4, plus hMN-14 (100 microg/dose) days 2, 3, 4, 5, 7, 8, 9, 10, 11, 15 and 22, then every 7 days until the animal died, the tumor attained a volume of 2 cm3, or the study terminated. Group 6: hMN-14 (confirm 100 microg/dose), days 2, 3, 4, 5, 7, 8, 9, 10, 11, 15 and 22, then every 7 days until the animal died, the tumor attained a volume of 2 cm3, or the study terminated. Animals were monitored for survival. Tumor and body weight were measured weekly. Results demonstrate that significant delays in tumor growth were caused by either MAb therapy alone or chemotherapy alone. The 75 microg dose of DTIC in combination with this schedule of hMN-14 antibody was significantly more effective than either treatment alone. The results of combined DTIC and MAb therapy were not additive. At 7 weeks, 8/10 mice in the 75 mug DTIC and MAb group had no palpable tumor, compared to 1/10 mice in the 75 microg DTIC only group and 0/10 mice in the untreated and MAb group. Mean tumor volumes at 7 weeks were 0.018+/-0.039 cm3 (75 microg DTIC plus MN-14), 0.284+0.197 cm3 (75 microg DTIC only), 0.899+/-0.545 cm3 (hMN-14 only) and 1.578+/-0.959 cm3 (untreated). Combined therapy of the naked anti-CEA antibody with DTIC augments the anti-tumor effects of antibody or chemotherapy alone, without increased toxicity.

MECHANISM OF ACTION - None given.

USE - (I) is useful for treating medullary thyroid carcinoma or non-medullary thyroid carcinoma such as pancreatic cancer, breast cancer, ovarian cancer, in a subject.

ADMINISTRATION - The MN-14 antibody or its fragment is administered in a dosage of 100-600, preferably 300 mg protein/dose/injection (claimed). (88 pages)

L9 ANSWER 4 OF 6 BIOTECHDS COPYRIGHT 2006 THE THOMSON CORP. on STN
AN 2004-13886 BIOTECHDS
TI Treating non-medullary or medullary thyroid carcinoma, involves administering to subject, either concurrently or sequentially, anti-carcinoembryonic antigen antibody or its fragment and therapeutic agent;
antibody against antigen for use in disease therapy
AU GOLDENBERG D M; HANSEN H J
PA IMMUNOMEDICS INC
PI WO 2004032857 22 Apr 2004
AI WO 2003-US31801 8 Oct 2003
PRAI US 2003-467161 2 May 2003; US 2002-416531 8 Oct 2002
DT Patent
LA English
OS WPI: 2004-340797 [31]
AN 2004-13886 BIOTECHDS
AB DERWENT ABSTRACT:

NOVELTY - Treating (M1) non-medullary or medullary thyroid carcinoma, comprising administering to a subject, either concurrently or sequentially, an anti-carcinoembryonic antigen (anti-CEA) antibody or its fragment and at least one therapeutic agent, and optionally formulated in a vehicle, is new.

DETAILED DESCRIPTION - Treating (M1) non-medullary or medullary thyroid carcinoma, involves administering to a subject, either concurrently or sequentially, an anti-carcinoembryonic antigen (anti-CEA) antibody or its fragment and at least one therapeutic agent, and optionally formulated in a vehicle.

Optionally, (M1) involves treating cancer by: (a) pre-treating a subject suffering from cancer with an anti-CEA antibody or its fragment prior to administration of the non-antibody therapeutic agent; (b) administering to a subject suffering from cancer, prior to administration of the antibody, an agent that activates granulocytes and/or NK cells in order to increase effector function of the antibody; or (c) administering to a subject suffering from cancer, prior to administration of the anti-CEA antibody or fragment, an amount of interferon effective to upregulate CEA expression in tumor cells. INDEPENDENT CLAIMS are also included for: (1) the composition (I) comprising at least one anti-CEA MAb (MAb) or its fragment and at least one therapeutic agent; and (2) an antibody fusion protein (II) comprising at least one CEA binding site and at least one other binding site for the same or different antigen.

BIOTECHNOLOGY - Preferred Method: In (M1), the anti-CEA MAb is a Class I, Class II or Class III anti-CEA MAb. The anti-CEA MAb is a Class I or Class II anti-CEA MAb, which is reactive with granulocytes and is a monovalent form of the MAb. The anti-CEA MAb or its fragment is humanized, where the humanized MAb retains substantially the anti-CEA binding specificity of a murine anti-CEA MAb. The anti-CEA MAb or its fragment is a chimeric MAb, which retains substantially the anti-CEA binding specificity of murine anti-CEA MAb. The anti-CEA MAb or its fragment is a MN-14 antibody or its fragment. The MN-14 MAb or its fragment comprises the complementarity-determining regions (CDRs) of a murine MN-14 MAb, where the CDRs of the light chain variable region of the MN-14 antibody comprises CDR1 having an amino acid sequence of Lys-Ala-Ser-Gln-Asp-Val-Gly-Thr-Ser-Val-Ala, CDR2 having an amino acid sequence of Trp-Thr-Ser-Thr-Arg-His-Thr and CDR3 having an amino acid sequence of Gln-Gln-Tyr-Ser-Leu-Tyr-Arg-Ser. The CDRs of the heavy chain variable region of the anti-CEA antibody comprises CDR1, CDR2 and CDR3 having Thr-Tyr-Trp-Met-Ser, Glu-Ile-his-Pro-Asp-Ser-Ser-Thr-Ile-Asn-Tyr-Ala-Pro-Ser-Leu-Lys-Asp and Lys-Tyr-Phe-Gly-Phe-Pro-Trp-Phe-Ala-Tyr, respectively. The anti-CEA MAb reacts with CEA and is unreactive with normal cross-reactive antigen (NCA) and meconium antigen (MA). The MN-14 MAb or its fragment is a humanized, chimeric or fully human MN-14 antibody or its fragment. The framework regions (FRs) of the light and heavy chain variable regions of the humanized MN-14 antibody or its fragment comprise at least one amino acid substituted from the corresponding FRs of a murine MN-14 MAb. The humanized MN-14 antibody or its fragment comprises at least one amino acid from the corresponding FR of the murine MN-14 antibody, chosen from amino acid residue 24, 28, 30, 48, 49, 74 and 94 of the murine heavy chain variable region designated as KLHuVhAIGA or (hMN-14). The humanized MN-14 antibody or its fragment comprises at least one amino acid from the corresponding FR of the murine MN-14 light chain variable region. The humanized MN-14 antibody or its fragment comprises the light chain variable region as set forth in (hMN-14) and the heavy chain variable region designated as KLHuVhAIGA, 15B (hMN-14) or 16B. The fragment is chosen from F(ab')2, Fab', Fab, Fv and sFV. The therapeutic agent is chosen from humanized, chimeric, human or murine MAb or its fragment chosen from Class I anti-CEA MAb, Class II anti-CEA MAb, Class III anti-CEA MAb, and its fragment, and is administered either concurrently or sequentially in a therapeutically effective amount. The therapeutic agent is either a naked antibody or an antibody conjugated to another therapeutic agent. The therapeutic agent is chosen from naked antibody, cytotoxic agent, a drug, a radionuclide, an immunomodulator, a photoactive therapeutic agent, an immunoconjugate of a CEA or non-CEA antibody, a hormone, or its combination, optionally formulated in a pharmaceutically acceptable vehicle. The therapeutic agent is chosen from humanized, chimeric, human or murine MAb or its fragment reactive with EGP-1, EGP-2 (e.g., 17-1A), IL-6, MUC-1, MUC-2, MUC-3, MUC-4, PAM-4, KC4, TAG-72, EGFR, EGP-2, HER2/neu, BrE3, Le-Y, A3, A33, EP-CAM, AFP, Tn, Thomson-Friedenreich antigens, tumor necrosis antigens, VEGF, tenascin, fibronectin, or other tumor angiogenesis antigens, Ga 733, and its combination, and is administered to the subject either concurrently or sequentially in a therapeutically effective amount. The antibody or its fragment is either naked or conjugated to another therapeutic agent. The therapeutic agent is not DTIC. The cytotoxic agent is a drug or a toxin. The drug possesses the pharmaceutical property chosen from the group consisting of antimitotic, alkylating, antimetabolite, antiangiogenic, apoptotic, alkaloid, COX-2, and antibiotic agents and its combinations. The drug is chosen from nitrogen mustards, ethylenimine derivatives, alkyl sulfonates, nitrosoureas, triazenes, folic acid analogs, anthracyclines, taxanes, COX-2 inhibitors, pyrimidine analogs, purine analogs, antimetabolites, antibiotics, enzymes, epipodophyllotoxins, platinum coordination complexes, vinca alkaloids, substituted ureas, methyl hydrazine derivatives, adrenocortical suppressants, antagonists, endostatin, taxols, camptothecins, doxorubicins and their analogs, and its combination. The toxin is a microbial, plant or animal toxin chosen from ricin, abrin, alpha toxin, saporin, ribonuclease (RNase), DNase I, Staphylococcal enterotoxin-A, pokeweed antiviral protein, gelonin, diphtherin toxin, Psuedomonas exotoxin, and Pseudomonas endotoxin. The immunomodulator is chosen from cytokine, a stem cell growth factor, a lymphotoxin, a hematopoietic factor (e.g., interleukin), a colony stimulating factor (CSF) (e.g., granulocyte-colony stimulating factor (G-CSF) or granulocyte macrophage-colony stimulating factor (GM-CSF)), an interferon (IFN) (e.g., interferons-alpha, -beta, or -gamma), a stem cell growth factor (designated S1 factor), erythropoietin, thrombopoietin and its combination. The lymphotoxin is tumor necrosis factor (TNF). The immunomodulator comprises IL-1, IL-2, IL-3, IL-6, IL-10, IL-12, IL-18, interferon-gamma, TNF-alpha or its combination. The radonuclide has an energy between 20-10000 keV.74. The radionuclide is chosen from 125I, 131I, 90Y, 88Y, 225Ac, 177Lu, 188Re, 186Re, and its combination. The photoactive therapeutic agent is a chromogen or dye. The alkylating agent is decarbazine. The Class III anti-CEA MAb or its fragment is humanized, which retains substantially the Class III anti-CEA binding specificity of a murine Class III anti-CEA MAb. The Class III anti-CEA MAb or is fragment is a chimeric MAb, which retains substantially the Class III anti-CEA binding specificity of murine Class III anti-CEA MAb. The Class III anti-CEA MAb or its fragment is a MN-14 antibody or its fragment. The humanized Class III anti-CEA antibody or its fragment is a humanized MN-14 antibody or its fragment. The therapeutic agent is chosen from humanized, chimeric, human or murine MAb or its fragment chosen from a Class I anti-CEA MAb, Class II anti-CEA MAb, Class III anti-CEA MAb, and its fragment, and is administered either concurrently or sequentially in a therapeutically effective amount. The therapeutic agent is either a naked antibody or an antibody conjugated to another therapeutic agent. The therapeutic agent is CPT-11. The anti-CEA antibody or its fragment administered prior to administration of CPT-11. The anti-CEA antibody or its fragment is administered around 3 days prior to administration of CPT-11. The therapeutic agent is DTIC, oxaliplatin or 5-flourouracil/leucovorin. The anti-CEA antibody is hMN-14. The therapeutic agent is CPT-11 or GM-CSF. Preferred Composition: In (I), the anti-CEA MAb or its fragment is a fully human MAb, which retains substantially the anti-CEA binding specificity of murine anti-CEA MAb. The chimeric MN-14 antibody or its fragment comprises the light chain variable region designated as murine MN-14 Vk and the heavy chain variable region designated as murine MN-14 VH. The fragment is chosen from F(ab')2, Fab', Fab, Fv and scFv. The combination comprises vincristine, doxorubicin, DTIC and cyclophosphamide. The therapeutic agent is a naked antibody or an immunoconjugate. Preferred Fusion protein: In (II), the CEA binding site binds to the same site as a Class I, II or III anti-CEA antibody. The CEA binding site binds to the same site as a Class III anti-CEA antibody. (II) is bivalent and trivalent. One arm of (II) is a Class III anti-CEA MAb that targets CD66e and another arm of (II) is from another anti-CEA cross-reactive antibody that targets CD66a-d. The binding sites are scFv or Fab regions. (II) is a bispecific, trivalent protein comprising one arm reactive with NCA50/90 and two arms reactive with only CEA. (II) is a bispecific protein comprising two arms that bind to NCA50/90. (II) is a diabody comprising one arm that binds to NCA50/90 and a second arm that binds to a Class III epitope of CEA. The NCA-50/90 arm is obtained from an hMN-3 antibody and the second arm that binds to a Class III epitope of CEA is obtained from hMN-14. (II) lacks an Fc-domain to prevent activation of cytokine release from granulocytes or which has an Fc-domain that has been modified to prevent complement fixation and ADCC. (II) is a triabody comprising one hMN-3 arm and two hMN14 arms or one hMN-15 arm and two hMN14 arms. (II) comprises at least one hMN-14 arm and at least one MN-6 arm. (II) further comprises an Fc-domain to enable complement fixation and activation of ADCC, or a therapeutic agent such as cytokine e.g., interferon, a colony-stimulating factor, or an interleukin. The colony-stimulating factor is GM-CSF or G-CSF.

ACTIVITY - Cytostatic.

MECHANISM OF ACTION - Antibody therapy; Stimulator of antibody-dependent cell-mediated cytotoxicity; Stimulator of complement-mediated lysis; Inhibitor of cell growth; Inhibitor of cell cycle progression; Stimulator of apoptosis; Inhibitor of angiogenesis. To detect the effect of naked hMN-14 CEA MAb and CPT-11 in an advanced cancer model, the following test was done. The hMN-14 was given to mice at a dose of 100 approximately mg/day over 14 days an then 2 times/week after it, starting on day 0 after tumor implantation. CPT-11 was given at 60 microg/day over 5 days. No effect of hMN-14 by itself is apparent under these conditions, and only a modest effect of CPT-11 was observed. HMN-14 increases the effect of CPT-11, as seen by comparing the CPT-11 median survival of 63 days against combination therapy median survival of 77 days. Combination therapy with hMN-14 CEA MAb and CPT-11 significantly prolongs survival of an animal with advanced human colonic tumor metastasis.

USE - (M1) is useful for treating non-medullary or medullary thyroid carcinoma (claimed).

ADMINISTRATION - 100-600 (preferably 300-400) milligrams protein per dose per injection of MN-14 antibody is administered by parenteral or subcutaneous route.

EXAMPLE - No suitable example given. (122 pages)

L9 ANSWER 5 OF 6 BIOTECHDS COPYRIGHT 2006 THE THOMSON CORP. on STN
AN 2004-03563 BIOTECHDS
TI New compound, useful for preparing a composition for diagnosing or treating tumor or infections caused by fungus, virus, parasite, bacterium, protozoan or mycoplasm;
for use in cancer and fungus, virus, parasitic, bacterium, protozoon and mycoplasm infection diagnosis and gene therapy
AU GOLDENBERG D M; HANSEN H; LEUNG S; MCBRIDE W J; QU Z
PA IMMUNOMEDICS INC; MCCALL J D
PI WO 2003097105 27 Nov 2003
AI WO 2003-GB2110 16 May 2003
PRAI US 2002-150654 17 May 2002; US 2002-150654 17 May 2002
DT Patent
LA English
AN 2004-03563 BIOTECHDS
AB DERWENT ABSTRACT:

NOVELTY - A compound, useful for preparing a composition for diagnosing or treating tumor or infections caused by fungus, virus, parasite, bacterium, protozoan or mycoplasm, comprising the formula (I), is new.

DETAILED DESCRIPTION - A compound, useful for preparing a composition for diagnosing or treating tumor or infections caused by fungus, virus, parasite, bacterium, protozoan or mycoplasm, comprising the formula (I): X-Phe-Lys(HSG)-D-Tyr-Lys(HSG)-Lys(Y)-NH2 (I) The compound includes a hard acid cation chelator at X or Y, and a soft acid cation chelator at remaining X or Y. INDEPENDENT CLAIMS are also included for: (1) a targetable construct; (2) a method of diagnosing or treating a disease or condition that may lead to a disease; (3) a method for detecting or treating target cells, tissues or pathogens in a mammal; (4) a method of treating or identifying diseased tissues in a subject; (5) a kit for treating or identifying diseased tissues in a subject; (6) a method for imaging normal tissue in a mammal; (7) a method of intra-operatively identifying diseased tissues in a subject; (8) a method for the endoscopic identification of diseased tissues in a subject; and (9) a method for the intravascular identification of diseased tissues in a subject.

BIOTECHNOLOGY - Preferred Compound: The compound comprises the formula: (a) (II) DOTA-Phe-Lys(HSG)-D-Tyr-Lys(HSG)-Lys(Tscg-Cys)-NH2; or (b) Tscg-Cys-Phe-Lys(HSG)-D-Tyr-Lys(HSG)-Lys(DOTA)-NH2. The compound further comprises at least one radionuclide, therapeutic agent or diagnostic agent. The radionuclide comprises 225Ac, 143pr, 223Ra, 82mRb, 186Re, 188Re, 189Re, 105Rh, 47Sc, 153Sm, 75Se, 83Sr, 89Sr, 161Tb, 86Y, 90y, 90Y, and 89Zr. When the targetable construct includes more than one radionuclide, the radionuclides may be different radionuclides. The hard acid cation chelator includes a carboxylate or amine group. It comprises NOTA, DOTA, DTPA, or TETA. It includes a cation consisting of Group IIa or Group IIIa metal cations. The soft acid cation chelator includes a thiol group. It comprises Tscg-Cys or Tsca-Cys. It includes a cation consisting of transition metals, lanthanides, actinides, Tc, Re or Bi. Preferred Construct: The targetable construct comprises X-Phe-Lys(HSG)-D-Tyr-Lys(HSG)-Lys(Y)-NH-R; where the targetable construct includes a hard acid cation chelator at X or Y, a soft acid cation chelator at remaining X or Y and a therapeutic agent, diagnostic agent or enzyme at R. R is covalently linked to the targetable construct by a linker moiety, where the linker moiety includes at least one amino acid. The therapeutic agent includes a radionuclide, drug, prodrug or toxin. The prodrug comprises epirubicin glucuronide, CPT-I 1, etoposide glucuronide, daunomicin glucuronide or doxorubicin glucuronide. The toxin is ricin, abrin, ribonuclease (RNase), DNase I, Staphylococcal enterotoxin-A, pokeweed antiviral protein, gelonin, diphtherin toxin, Pseudomonas exotoxin or Pseudomonas endotoxin. The diagnostic agent includes one or more agents for photodynamic therapy, preferably a photosensitizer consisting of benzoporphyrin monoacid ring A (BPD-MA), tin etiopurpurin (SnET2), sulfonated aluminum phthalocyanine (A1SPc) or lutetium texaphyrin (Lutex). The diagnostic agent comprises one or more image enhancing agents for use in magnetic resonance imaging (MRI). The enhancing agents include Mn, Fe, La or Gd. The diagnostic agent comprises one or more radiopaque or contrast agents for X-ray or computed tomography. The radiopaque or contrast agents include barium, diatrizoate, ethiodized oil, gallium citrate, iocarmic acid, iocetamic acid, iodamide, iodipamide, iodoxamic acid, iogulamide, iohexol, iopamidol, iopanoic acid, ioprocemic acid, iosefamic acid, ioseric acid, iosulamide meglumine, iosemetic acid, iotasul, iotetric acid, iothatamic acid, iotroxic acid, ioxotrizoic acid, ipodato, meglumine, metrizam/de, metrizoate, propyliodone or thallous chloride. The diagnostic agent comprises one or more ultrasound contrast agents. The ultrasound contrast agent includes a liposome or dextran. The liposome is gas-filled. The enzyme includes an enzyme capable of converting drug intermediate to a toxic form to increase toxicity of the drug at a target site. Preferred Kit: The kit for treating or identifying diseased tissues in a subject comprises: (a) a targetable construct comprising the compound; (b) a bi-specific antibody or antibody fragment having at least one arm that specifically hinds a targeted tissue and at least one other arm that specifically binds the targetable construct; and optionally (c) a clearing composition useful for clearing non-localized antibodies and antibody fragments. Preferred Method: Diagnosing or treating a disease or condition that may lead to a disease comprises: (a) administering to the subject a bi-specific antibody or antibody fragment having at least one arm that specifically binds a targeted tissue and at least one other arm that specifically binds a targetable construct; (b) optionally, administering to the subject a clearing composition, and allowing the composition to clear non-localized antibodies or antibody fragments from circulation; and (c) administering to the subject a targetable construct comprising the compound. The bi-specific antibody or antibody fragment has at least one other arm that specifically binds a targeted tissue and at least one other arm that specifically binds a targetable construct and the targetable construct are administered at substantially the same time. The therapeutic cation emits particles and/or positrons having 20 to 10000 keV. The therapeutic cation is 194Ir, 198Au, 199Au or 211pb. The diagnostic cation emits particles and/or positrons having 25-10000 keV. The diagnostic cation is 110In, 177La, 18F, 52Fe, 62Cu, 64Cu, 67Cu, 67Ga, 68Ga, 86y, 90y, 89Zr, 94mTc, 94Tc, 99roTc' 1201, 123i, I24I, 125I, 1311, 154-158Gd' 32p, llc, 13N, 150, 186Re, 188Re, 52mMn, 55Co, 72As, 75Bt, 76Br, 82mRb or 83Sr. The diagnostic agent is used to perform positron-emission tomography (PET) or SPECT imaging. The diagnostic agent comprises one or more ultrasound contrast agents, which includes a liposome or dextran. The liposome is gas-filled. The diagnostic agent comprises fluorescent compound, a chemiluminescent compound or a bioluminescent compound. The targeted tissue is a tumor. The tumor produces or is associated with antigens consisting of colon-specific antigen-p (CSAp), carcinoembryonic antigen (CEA), CD19, CD20, CD21, CD22, CD23, CD30, CD74, CDS0, HLA-DR, Ia, MUC 1. MUC 2, MUC 3, MUC 4, EGFR, HER 2/neu, PAM-4, TAG-72, EGP-I, EGP-2, A3, KS1, Le(y), S100, PSMA, PSA, tenascin, relate receptor, VEGFR, necrosis antigens, IL-2, T101 or MAGE. The at least one arm that specifically binds a targeted tissue or targetable construct is a monoclonal antibody, human, chimeric or humanized antibody or its fragment. The bi-specific antibody or antibody fragment further comprises a therapeutic nuclide. The bi-specific antibody comprises the Fv of Mab Mu-9 and the Fv of MAb 679. Mu-9 and/or 679 ere chimerized or humanized or human Mu-9 and 679. The bi-specific antibody comprises one or more of the CDRs of Mu-9 or 679. The bi-specific antibody is a fusion protein. The bi-specific antibody comprises the Fv of Mab MN-14 and the Fv of MAb 679. MN-14, and/or 679 are chimerized or humanized or are human MN-14 and 679. The bi-specific antibody comprises one or more of the CDRs of MN-14 or the CDRs of 679. The fusion protein is trivalent, and incorporates the Fv of an antibody reactive with CSAp. The bi-specific antibody incorporates a Class -III anti-CEA antibody and the Fv of 679. The targetable construct comprises one or more radioactive isotopes useful for killing diseased tissue. The targetable construct comprises 10B atoms. The method further comprises the step of irradiating the boron atoms localized at the diseased tissue, thereby effecting BNCT of the diseased tissue. The targetable construct comprises an enzyme. The method further comprises administering to the subject a drug which the enzyme is capable of converting to a toxic form, and, therefore, increasing the toxicity of the drug at the target site. Detecting or treating target cells, tissues or pathogens in a mammal comprises administering the bi-specific antibody or antibody fragment comprising at least one arm that specifically binds a target and at least one other arm that specifically binds a targetable construct and administering a targetable construct comprising the compound; where the target includes a target cell, tissue, pathogen or a molecule produced by or associated with it and at least one arm that specifically binds the target is capable of binding to a complementary binding moiety on the target. The pathogen is a fungus, virus, parasite, bacterium, protozoan or mycoplasm. The fungus is Trichophyton, Epidermophyton, Sporothrix schenckii, Cryptococcus neoformans, Coccidioides immitis, Histoplasma capsulatum, Blastomyces dermatitidis or Candida albicans. The virus is HIV, herpes v/ms, cytomegalovirus, rabies virus, influenza virus, hepatitis B virus, Sendai virus, feline leukemia virus, polio virus, human serum parvo-like virus, simian virus 40, respiratory syncytial virus, mouse mammary tumor virus, Varicella-Zoster virus, Dengue virus, rubella virus, measles virus, adenovirus, human T-ceil leukemia viruses, Epstein-Ban: virus, murine leukemia virus, mumps virus, vesicular stomatitis virus, Sindbis virus, lymphocytic choriomeningitis virus, wart virus or blue tongue virus. The bacterium is Anthrax bacillus, Streptococcus agalactiae, Legionella pneumophilia, Streptococcus pyogenes, Escherichia coil, Neisseria gonorrhoeae, Neisseria meningitidis, Pneumococcus, Hemophilus influenzae B, Treponema pallidum, Lyme disease spirochetes, Pseudomonas aeruginosa, Mycobacterium leprae, Brucella abortus, Mycobacterium tuberculosis or Tetanus toxin. The parasite is a helminth or a malarial parasite. The protozoan is Plasmodium falciparum, Plasmodium vivax, Toxoplasma gondii, Trypanosoma rangeli, Trypanosoma cruzi, Trypanosoma rhodesiensei, Trypanosoma brucei, Schistosoma mansoni, Schistosoma japonicum, Babesia bovis, Elmeria tenella, Onchocerca volvulus, Trichinella spiralis, Onchocerca volvulus, Theileria parva, Taenia ovis, Taenia saginata or Mesocestoides corti. Treating or identifying diseased tissues in a subject comprises administering to the subject a bi-specific antibody or antibody fragment, a targetable construct comprising the compound or optionally, a clearing composition, and allowing the composition to clear non-localized antibodies or antibody fragments from circulation. The subject comprises humans, primates, equines, canines or felines. Imaging normal tissue in a mammal comprises administering bi-specific antibody or targetable construct comprising the compound. The normal tissue is tissue from the ovary, thymus, parathyroid, endometrium, hone marrow or spleen. intra-operatively identifying diseased tissues in a subject comprises administering bi-specific antibody or antibody fragment and a targetable construct comprising the compound. Endoscopic or intravascular identification of diseased tissues in a subject comprises administering bi-specific antibody or antibody fragment and a targetable construct comprising the compound.

ACTIVITY - Cytostatic; Virucide; Antifungal; Antiparasitic; Antibacterial; Protozoacide. No biological data given.

MECHANISM OF ACTION - Gene therapy.

USE - The compound is useful for preparing a composition for diagnosing or treating tumor or infections caused by fungus, virus, parasite, bacterium, protozoan or mycoplasm (claimed).

EXAMPLE - No relevant examples given.(119 pages)

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AN 1983:13193866 BIOTECHNO

TI Immunological heterogeneity of carcinoembryonic antigen: Antigenic determinants on carcinoembryonic antigen distinguished by monoclonal antibodies

AU Primus F.J.; Newell K.D.; Blue A.; Goldenberg D.M.

CS Div. Exp. Pathol., Dep. Pathol., Univ. Kentucky Med. Cent., Lexington, KY 40536, United States.

SO Cancer Research, (1983), 43/2 (686-692)
CODEN: CNREA8

DT Journal; Article

CY United States

LA English

AB Murine monoclonal antibodies against carcinoembryonic antigen (CEA) derived from a colonic tumor were analyzed by radioimmunoassay for reactivity with CEA and the CEA-related antigens, meconium antigen (MA) and nonspecific cross-reacting antigen. Antibody-antigen binding profiles revealed three classes of hybridomas. The Class I antibody, NP-1, recognized an epitope shared among all three antigens, and its affinity for CEA and MA was high but low for nonspecific cross-reacting antigen. The Class II antibodies reacted with sites shared between CEA and MA, while those of the Class III type only bound CEA. The
Class III antibody, NP-4, bound less than 50% of the
CEA molecules recognized by goat specific anti-CEA

antibody and the other classes of monoclonal antibodies. Two Class II antibodies, NP-2 and NP-3, bound similar amounts of CEA and MA with moderate but different affinities for CEA. Studies using labeled monoclonal antibodies for CEA epitope blocking revealed that NP-2 and NP-3 recognize two separate epitopes on CEA within the Class II category. Thus, monoclonal antibodies to CEA can differentiate at least four antigenic sites on colonic cancer CEA. One is shared by CEA, MA, and nonspecific cross-reacting antigen; two others are shared by CEA with MA; and a fourth appears specific for a subpopulation of CEA molecules.

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#6	Search **anti-CEA antibody and class III** Limits: **Publication Date to 2002/10/8**	15:44:30	2
#5	Search **anti-CEA antibody** Limits: **Publication Date to 2002/10/8**	15:44:21	802
#3	Search **Mn-14 and CPT-11** Limits: **Publication Date to 2002/10/8**	15:12:24	2
#2	Search **Mn-14 and cytotoxic** Limits: **Publication Date to 2002/10/8**	15:11:16	1
#1	Search **Mn-14 and cytotoxic agent** Limits: **Publication Date to 2002/10/8**	15:10:52	0

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☐	L8	L7 and CPT-11	2
☐	L7	(MN-14 antibody)	17
☐	L6	L5 and cyclophosphamide	17
☐	L5	L4 and DTIC	17
☐	L4	L3 and doxorubicin	31
☐	L3	L2 and vincristine	31
☐	L2	L1 and CPT-11	44
☐	L1	MN-14 and antibody and cytotoxic	90

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	DB=PGPB,USPT,USOC,EPAB,JPAB,DWPI; PLUR=YES; OP=ADJ		
☐	L8	L6 and cyclophosphamide	18
☐	L7	L6 and DTIC	2
☐	L6	L5 and doxorubicin	18
☐	L5	L4 and CPT-11	18
☐	L4	L3 and vincristine	37
☐	L3	anti-CEA antibody and cytotoxic agent	114
☐	L2	ant-CEA antibody and cytotoxic agent	0
☐	L1	wo 2003097105	1

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